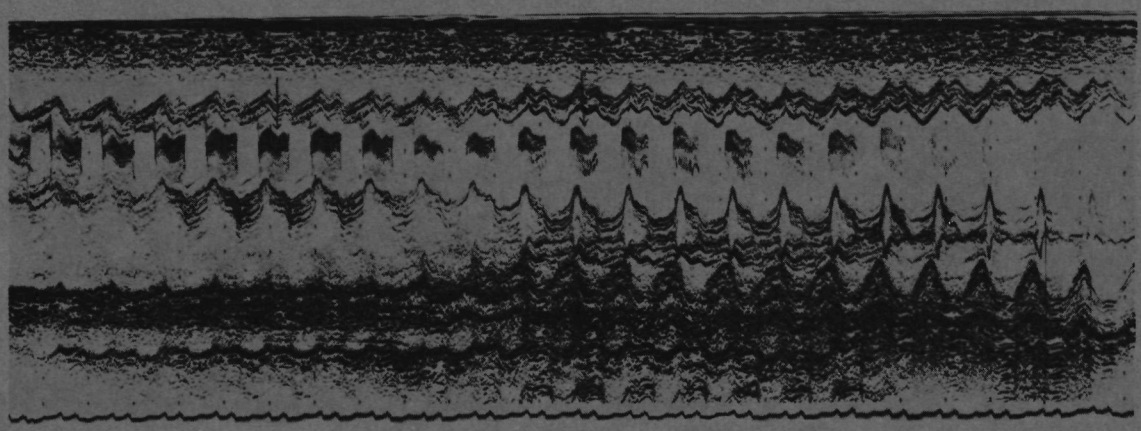
infective endocarditis and cardiac surgery



karel van leeuwen

INFECTIVE ENDOCARDITIS AND CARDIAC SURGERY

PROEFSCHRIFT

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As long as there are forests in the world, and lovers in those forests, the heart, as a symbol of love, will exist. Indeed, on how many thousands, if not millions, of trees throughout the universe has a lover carved, with a penknife, with trembling hand, a heart pierced through by an arrow, and in that heart, all his love, with simple words. (N. Boyadjian: The Heart).

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Chapter 1

INTRODUCTION

Prior to the antibiotic era, infective endocarditis was an almost universally fatal disease. The introduction of sulfonamides saved a small proportion of patients suffering from this disease. In October, 1940, an American physician, M.H. Dawson, was the first to administer penicillin parenterally to a patient with streptococcal endocarditis. The patient was cured. The subsequent widespread use of penicillin dramatically increased survival. Despite the availability of this and other potent antibiotic drugs, infective endocarditis remains a serious disease and its management a therapeutic challenge. Certain subgroups of patients with this disease continue to have an unfavorable prognosis. The pioneering efforts of several surgeons in the 1960's established the validity of cardiac operation, even during the active phase of infective endocarditis, in those patients with clinical findings presaging a poor outcome. This investigation was carried out to review our experience with the surgical management of patients with complicated infective endocarditis.

The following questions will be answered.

1. How many adult patients underwent cardiac surgery in the St. Radboud Hospital in Nijmegen in the last 10 years during or after infective endocarditis, and what type of surgery was performed?
2. What was the clinical presentation and course of infective endocarditis?
3. What were the indications for cardiac surgery?
4. What was, in retrospect, the most reliable diagnostic aid in the assessment of cardiac anatomy as revealed by operative findings?
5. What were the results in regard to: a) mortality; b) morbidity; c) pathological-bacteriological examination of surgically removed material; and d) long-term outlook?

6. What suggestions are there for optimal treatment with respect to: a) surgical indication and timing; b) pre-operative investigation; and c) postoperative care?

2.1. Definition and terminology

Infective endocarditis (IE) is defined as infection of the endocardium. The infective lesion may be situated on a heart valve or on mural endocardium. The cause of this infection can be bacterial (most common), fungal and sometimes rickettsia (Coxiella burneti) or viral infection (Coxsackie B virus). The terms "acute" and "subacute" endocarditis arose in the pre-antibiotic era when all or virtually all patients with IE died. They referred to the time periods between onset of symptoms or signs of IE and death. Acute indicated a time course < 6 weeks (Kaye, 1976). Antibiotics have changed these time courses and therefore these terms are no longer proper. Both terms also have been used to indicate the type of infecting organism: the α-hemolytic streptococcus causing the subacute variety (usually on a deformed heart valve), while aggressive micro-organisms like staphylococcus aureus, pneumococcus or gram-negative organisms caused the acute form of infective endocarditis with rapid and severe valve destruction (on often normal cardiac valves prior to infection). However, in the individual patient these relationships often break down and antibiotic therapy may alter the virulence of certain micro-organisms. For example streptococcus viridans can cause IE with an acute course on normal valves, whereas staphylococcus aureus can cause IE with a subacute course. It is currently of more practical importance to classify IE according to causative micro-organisms (Kaye, 1976).

2.2. Pathogenesis

Presence of micro-organisms in the blood is required for endocarditis to occur. They may enter into the bloodstream from the oropharynx, genitourinary and gastrointestinal tracts, lungs or skin. An infected focus is not a requisite since

transient bacteremia can occur spontaneously in normal individuals (Hocket et al, 1972) or after simple procedures as tooth brushing or chewing hard candy (Cobe, 1954). Once bacteremia occurs the heart valve can be infected in 2 ways:
1. via blood vessels in the substance of the valve
2. by direct deposition on the endothelial surface.
As valves are vascularised only at the proximal parts and since this location does not correspond to the usual sites of vegetations on the valve (the free edges), the most widely accepted view is that micro-organisms are deposited on the endocardial surface via the blood in the main circulation. Angrist and Oka (1963) developed the concept that the initial lesion is that of non-bacterial thrombotic endocarditis (NBTE), characterized by aggregates of platelets and fibrin. The common factor of formation of this NBTE is alteration of the endothelium as occurring on a previously damaged cardiac valve. Minimal endothelial damage is sufficient to cause accumulation of platelets (Ashford and Freiman, 1967). Fibrin is laid down in contact with the platelets thus stabilising the aggregates.
Especially heart valves are susceptible to NBTE as they contain much collagen (a potent stimulus to platelet aggregation) and are subject to more movement, mechanical stress and trauma than other parts of the endocardium. The sterile endothelial vegetation forms a suitable surface for the circulating bacteria, which may adhere directly or may be taken up by phagocytes located on the vegetation. Thus the sterile vegetation is converted into an infected vegetation in which bacteria can rapidly grow and give rise to a continuous bacteremia. Endothelial damage occurs in patients with valvular disease of congenital, rheumatic, degenerative or connective tissue origin. This is the patient group at risk of developing infective endocarditis. The infected vegetations in this group of patients are nearly always seen in the same location, for example, on the ventricular surface of the aortic valve in aortic regurgitation, on the atrial surface of the mitral valve in mitral regurgitation, in the case of ventricular septal defect on the right side of the defect and in the patients with coarctation

of aorta on the down stream wall. Rodbard (1963) demonstrated by injecting a bacterial aerosol into the air stream passing through an agar venturi tube how bacterial colonies were characteristically distributed in a collar-like way in the low-pressure sink immediately beyond the orifice. A venturi effect is thus produced by blood being driven from a high-pressure source (aorta, left ventricle, central aorta) through an orifice (respectively a nearly closed and regurgitant aortic valve or mitral valve, ventricular septal defect, coarctation) into a low-pressure sink (respectively left ventricle, left atrium, right ventricle, distal aorta). Satellite ("jet") lesions can occur on chordae tendineae in the case of aortic regurgitation, on the atrial wall in mitral regurgitation (McCallum's patch) and on the right ventricular wall opposite the defect in ventricular septal defect. The greater pressure exerted on the valves on the left side, and subsequently easier occurring endothelial lesion account for the much more frequently occurring left-sided endocarditis.

Another factor is the more frequent occurrence of underlying disease of the left side heart valves. An exception is the more frequent occurrence of right-sided endocarditis in narcotic addicts, probably caused by the repetitive trauma of the endothelial surface of the right-sided heart valves (especially the tricuspid valve) secondary to intravenous injection of contaminated material.

The NBTE theory does not explain the acute illness affecting previously normal valves and caused, for example, by staphylococcus aureus. Studies from Holmes et al (1977) and Gould et al (1975) pointed out that various bacteria have various adherence to surface of valves. In vitro studies of canine and human valvular leaflets showed that the degree of adherence on these valves was the highest with enterococcus and staphylococcus, followed by streptococcus viridans and staphylococcus albus, and was the lowest with Escherichia coli and Klebsiella pneumoniae. The poor adherence of E.coli may account for the low incidence of IE with this micro-organism despite the well-known high frequency of septicaemia.

Prostheses in the heart predispose to post-operative endocarditis. The incidence of endocarditis complicating the insertion of prosthetic valves is about 2%-4% (Weinstein and Rubin, 1973). Sutures, patches and valves are at risk of infection because they are avascular and thus partially inaccessible to host defenses. In addition, the tissue adjacent to the prosthesis may be damaged by the operative procedure, thus favoring the formation of NBTE and subsequent infection (Amoury et al, 1966).

2.3. Diagnosis

A definite diagnosis of IE can only be made by the bacteriologic or histologic identification of micro-organisms in material obtained from surgery or autopsy. A clinical diagnosis can be made on the basis of clinical features and certain diagnostic aids.

2.3.1. Clinical features

In its pure and uncomplicated form IE is characterized by multiplication of the etiological micro-organism at the endocardial surface with a resultant local acute and chronic inflammatory reaction. Strictly speaking, all of the other sequelae of this disorder can be regarded as "complications". Hence the clinical features of IE are related to the infection itself, the non-cardiac complications and the cardiac complications.

2.3.1.1. Features related to the infection itself

Fever is the most common sign in IE. The course of the febrile response, however, may be variable. As has been stated, there is a continuum between acute and subacute IE rather than a division; nevertheless a distinction can be made here. Patients with acute IE are often extremely ill with high fever, nausea, anorexia, headaches, dyspnea or chest pain. Medical advice is sought within weeks and sometimes within hours or days. On the other hand, the patient with subacute IE often has low-grade

fever and vague symptoms: weakness, fatigability, weight loss, malaise; a heart murmur is more likely to be present than in the acute disease. Only one of 167 patients with subacute and 7 of 54 patients with acute endocarditis have been reported by Pankey (1961, 1962) to be free of murmurs. He noted that changes in the character of the murmur occurred in 16.7% of the subacute cases and in 7.4% of those with the acute form of infection. In contrast to the patient with acute disease the patient with subacute endocarditis comes to medical attention often weeks or months after the beginning of the symptoms.

2.3.1.2. Non-cardiac complications

1. Skin lesions: petechiae, subungual hemorrhages, Osler nodes and Janeway lesions. Petechiae are tiny, purpuric hemorrhages of pin-point or pin-head size. They are due to defects of the capillary endothelium caused by the infection (Davidson, 1965). They occur in 19-40% of the cases (Weinstein and Rubin, 1973). The conjunctiva and oral mucosa are involved frequently; they also tend to occur in the dorsa of hands and feet, anterior chest and abdominal wall.
   Subungual hemorrhages are uncommon. The splinter hemorrhage has a linear form, its distal end does not reach the anterior edge of the nail bed. It has been suggested that the only clinically significant "splinter" hemorrhages are those that appear, in the absence of trauma, while patients are under observation (Dowling, 1964).
   Osler nodes are small erythematous lesions on the palms of the hands or soles of the feet or on the tips of fingers or toes. The most characteristic feature is tenderness. They are generally transient, lasting from hours to days. The lesions are seen in 10%-23% of patients with subacute IE and only rarely in acute IE (Weinstein and Rubin, 1973). Histologic study has revealed them to be areas of necrotizing vasculitis of the dermal glomus body (von Gemmingen and Winkelmann, 1967).
   Janeway lesions are small (1 to 4 mm in diameter) irregular, flat, erythematous, non-tender macules on the palms of the

hands and soles of the feet. The lesions blanch with pressure and elevation of the extremities. They occur in up to 5% of cases.

2. Central nervous system disorders. Neurologic or psychiatric symptoms and findings are common in IE, and if sought for may be found in up to 40% of patients with IE. Complications are mainly due to infected emboli; meningoenchephalitis is the most common complication, but major cerebral emboli and (bleeding) mycotic aneurysms are not rare. Brain abscesses are a more common complication in acute rather than subacute infective endocarditis. Other, less well characterized pathological complications include cerebral micro-infarcts, purpura and edema as well as endarteritis with thrombosis. A wide range of presentations can result from the cerebral lesions, the most dramatic being hemiplegia, afasia, cranial nerve paralysis, cerebral hemorrhage and subarachnoid hemorrhage (Ziment, 1969).
3. The eyes are involved in 11% of IE patients, often associated with neurologic involvement. Visual disturbances can result from papil edema, retinal hemorrhages, iridocyclitis or panophthalmitis. Sometimes partial or complete blindness of one eye can occur because of central retinal artery occlusion (Ziment, 1969). Fundoscopic examination should always be performed in a patient with (suspected) IE. The most common occurring retinal lesions are petechiae; in 2 to 4% of the cases a Roth spot can be seen. This lesion, first described by Roth (1872), has the appearance of a cotton-wool exudate. Histological study of these lesions has shown them to be composed of perivascular collections of lymfocytes in the nerve fiber layer of the retina, surrounded by edema and hemorrhage (Weinstein, 1980).
4. Musculoskeletal manifestations. Diffuse arthralgias occur in about 25%, often with small effusions in the joints. Clubbing of fingers and/or toes is found in 12 to 52% of the cases, almost exclusively in the subacute disease (Weinstein and Rubin, 1973).
5. The gastro-intestinal system can be affected by embolization with subsequently bowel infarction.

6. Splenomegaly. Lerner and Weinstein (1966) noted a palpable spleen in 44% of patients with subacute and in 23% of patients with acute infections. If the spleen infarcts, left upper quadrant pain may result.
7. Renal disease. In addition to emboli 2 other lesions may involve the kidney in the course of infective endocarditis. These are focal "embolic" glomerulonephritis and diffuse proliferative glomerulonephritis. An antigen-antibody complex mechanism for both forms of nephritis is supported by the demonstration by Williams and Kunkel (1962) of immune-complexes in the circulation of these patients. The incidence of renal insufficiency is about 10%. It may result from either focal or diffuse glomerulonephritis (Wilson et al, 1978).
8. Mycotic aneurysms. The overall incidence is approximately 15%. They may arise anywhere in the arterial system, from the aorta to a periferal arteriolus. Most periferal mycotic aneurysms develop at narrowings, bifurcations or sharp turns in the arteries. The pathogenetic mechanism in the formation of these aneurysms may be direct infection of the vascular endothelial surface or embolization to the vasa vasorum of an artery, resulting first in micro-abscess formation and later in mycotic aneurysm. Whatever the precise etiology, these aneurysms may be a serious and even lethal complication of IE (Snow and Cobbs, 1976).
9. Embolization. The overall incidence of emboli from lesions on the left side of the heart is 15% to 35%. The most common sites involved are the central nervous system, coronary vessels, spleen and kidney. Large emboli may occur in fungal endocarditis (Snow and Cobbs, 1976). In patients with right-sided endocarditis, particularly complicating intravenous drug abuse, pulmonary embolism dominate the clinical features. Banks et al (1973) reported pulmonary embolism in 64% of narcotic addicts with tricuspid endocarditis.

2.3.1.3. Features related to cardiac complications

IE is one of the most destructive cardiac events. The following

complications can occur:

1. Valvular damage.
   Hemodynamically significant valvular injury is the most important cardiac complication of IE and is characteristically manifested as regurgitation. The mechanism of valvular regurgitation is destruction of valve substance directly, or rupture of supporting structures of the valve, such as valve annulus, chordae tendineae or papillary muscles. Rarely vegetations may become sufficiently large to obstruct a valvular orifice and cause stenosis. Especially in patients with fungal endocarditis, large bulky vegetations can occur which may be greater than 8 cm^3 (McLeod and Remington, 1978). When virulent micro-organisms such as staphylococcus aureus attack previously normal valves, the hemodynamic consequences of acute insufficiency may be much more severe than when previously damaged valves are infected by less virulent bacteria (Snow and Cobbs, 1976). The mitral valve, especially the anterior leaflet and its chordae tendineae, may become involved in aortic valve endocarditis by the regurgitant jet through the incompetent aortic valve. This "jet"- or "drop"-lesion may cause perforation of the anterior mitral valve leaflet or rupture of its supporting chordae tendineae.
2. Localized suppuration.
   One of the most serious intracardiac complications of IE is the development of abscesses, which are present in about 20% in necropsy studies (Weinstein and Schlesinger, 1974). This complication is most common in patients with staphylococcal endocarditis. Abscesses may occur in any portion of the myocardium, but the so-called paravalvular "valve ring" abscesses are the most common. These occur by direct extension from a valvular focus to the valvular ring. In a necropsy study of 74 patients with active IE limited to one or both left-sided cardiac valves, Roberts (1978) found a valve ring abscess in 24 patients (32%): in 22 (92%) the ring abscess involved the aortic valve and in only 2 (8%) the mitral valve. Each of the 24 patients had valvular regurgi-

tation from IE. This kind of abscess may extend to the upper part of the interventricular septum and cause either atrioventricular conduction abnormalities (from first degree block to complete heart block) or intraventricular conduction defects (right or left bundle branch block). A myocardial abscess may rupture into the pericardial sac causing pericarditis or cardiac tamponade, or when it is located in the interventricular septum into the right ventricle or right atrium (ventriculo-atrial fistula) thus producing a left to right shunt. Sometimes the inflammation may extend into the sinus of Valsalva causing a local mycotic aneurysm. When such a sinus of Valsalva aneurysm ruptures, the manifestations depend primarily on the site of the aneurysm. A posterior (non-coronary) aortic sinus aneurysm may rupture into right or left atrium; a right aortic sinus aneurysm to right ventricle or right atrium; a left aortic sinus aneurysm into the pericardium (causing cardiac tamponade) or pulmonary trunk (CIBA-atlas of the heart). When the fibrous atrioventricular body is involved in the infection a false aneurysm of the left ventricle may develop (Chesler et al, 1968).

3. Myocardial infarction.
   Evidence of myocardial infarction has been found at necropsy in 40% to 60% of the cases of endocarditis many of which remained undetected during life. Embolic occlusion of one of the coronary arteries is the most common cause of infarction, especially in patients with aortic valve disease, but thrombosis of a coronary artery (secondary to a site of adjacent inflammation such as a nearby myocardial abscess) and mycotic aneurysm formation may also lead to infarction (Weinstein and Rubin, 1973).
4. Myocarditis.
   Myocardial inflammatory lesions are frequently seen in patients with IE at necropsy studies. These lesions were observed in 85% of 66 patients in whom numerous histologic sections of myocardium were examined by Roberts (1978). The significance of myocardial lesions in these patients has

been debated. Correl et al (1951) consider the lesions to be a major cause of congestive heart failure in patients with active IE. Perry et al (1952), however, believe that congestive heart failure is rarely the result of myocardial lesion. In none of the 66 patients with active IE studied at necropsy by Roberts (1978) was congestive cardiac failure attributed to the myocardial inflammatory lesions.

5. Pericarditis.
   This complication is most often seen in the acute type of (aortic valve) infection, is often purulent and results from extension of inflammation from a valve ring abscess, myocardial abscess, septic coronary artery embolus and sometimes from rupture of a mycotic aneurysm of the sinus of Valsalva (Weinstein, 1980).

Thus far all these complications have been discussed as a consequence of the active process. The healing process, however, can also play a role in damaging valves. When the acute phase is survived, usually by means of treatment, the ingrowth of blood vessels and proliferation of fibroblasts proceeds, the bacteria are cleared away and granulocytes are replaced by lymphocytes, plasma cells and macrophages. With organization (of the vegetation and inflammation of valvular tissue), the ulcerated surface becomes endothelialized, and granulation tissue appears at the margins of the lesions (Spain, 1968). This may lead to adhesion between cusps as the newly formed connective tissue becomes more fibrous and collagenous and shrinks. The progressive scarring of valves may cause increasing degrees of regurgitation and, in the healing phase of endocarditis, valve replacement may be necessary because of progressive heart failure due to valvular insufficiency (Eulderink, 1981).

2.3.2. Diagnostic aids

The following techniques are more or less useful in the diagnosis of IE.

2.3.2.1. Blood cultures

Studies on the nature of bacteremia of endocarditis have shown that the bacteremia is qualitatively continuous, but quantitatively discontinuous: organisms are probably always present, but their numbers vary considerably. The magnitude of the bacteremia ranges from less than 5 to more than 300 organisms per ml of blood (Werner et al, 1967). The incidence of positive blood cultures varies considerably. In the series described by Werner et al (1967), the blood culture was positive in 95% of 789 cultures in 206 cases of endocarditis. In 98% of the cases one of the first two cultures was positive and in 91% all blood cultures were positive. Previous antibiotic therapy resulted in a small but statistically significant reduction in the proportion of positive blood cultures. The incidence of positive blood cultures was 97% in those cases in which the patients had not received any antimicrobial agent within the two week period prior to blood culture, but was 91% ($P < 0.02$ by Chisquare analysis) in those cases in which the patients had received an antimicrobial agent during this period. Belli and Waisbren (1956) found only 53% incidence of positive blood cultures in 74 patients with IE. A possible explanation for the apparent discrepancy between these two studies could have been a difference in the technique of blood culture. The first authors took 10 ml of blood for culture, whereas the other authors used only 5 ml per culture. Considering the low order of magnitude of bacteremia 5 ml of blood might have been too small an amount. The true figure of culture negative endocarditis is probably about 15% (Weinstein and Rubin, 1973). A number of factors are responsible for sterile blood cultures such as: inadequate microbiologic methodology (improper media, failure to culture anaerobically and inadequate duration of incubation) and previous antimicrobial therapy. The general recommandation is to obtain 5 or 6 cultures of venous blood over a 24 hour period. (O'Keefe and Gorbach, 1978). In seriously ill patients in whom rapid initiation of therapy is important, 5 blood cultures spaced over 2 hours must be taken. Multiple blood cultures over several days may be necessary, up to

7 days after therapy has been withdrawn. Ten ml of blood should be drawn for culture and the optimal ratio of blood to medium is about 1:10. The blood must be devided between aerobic and anaerobic media. The cultures should be saved for at least two, preferably three, weeks. If antimicrobial therapy has been given during the previous 2 weeks, antibiotic therapy must be stopped and penicillinase can be added to the culture medium when penicillin or cephalosporin drugs have been administered. The penicillinase should be checked periodically for sterility, however, in order to avoid false positive blood cultures. Specialised media should be used in suspected fungemia. There appears to be no advantage in obtaining arterial over venous blood, since bacteria pass with ease through the capillary circulation (O'Keefe and Gorbach, 1978).

2.3.2.2. Other laboratory findings.

Elevation of the erythrocyte sedimentation rate is present in 90%-100% of the cases. Anemia occurs in 50%-80% and is usually normocytic and normochromic; hemolytic anemia rarely accompanies endocarditis. The periferal leukocyte count is often normal; "shift to the left" (occurrence of relatively more young myeloid cells in the periferal blood) is however common. Thrombocytopenia may be a feature of the acute form of the disease and is due to dissiminated intravascular coagulation or increased consumption of platelets (Weinstein and Rubin, 1973). In patients with a more chronic disease, there is often a reversal of the albumin globulin ratio due to hyperglobulinemia accompanied by an increase in numbers of plasma cells in the bone marrow, sometimes to a level approaching that observed in multiple myeloma. A positive rheumatoid factor occurs in up to 50% of patients with IE and is highly correlated with the duration of the disease (Williams and Kunkel, 1962). Circulating immunecomplex titers are often elevated. In a study of Cabane et al (1979) circulating immunecomplexes were found to be positive during the active phase of IE in 84% of the 64 patients studied. They conclude that detection of circulating immunecomplexes is useful for the diagnosis and the monitoring

of IE, particularly when blood cultures are negative. Gross or microscopic hematuria occurs in 30%-50%. Proteinuria is more common, occurring in 50%-65% (Mandell, 1976).

2.3.2.3. Radiography.

Chest X-ray findings are usually not impressive until destruction of a left-sided cardiac valve is so far advanced that congestive failure develops. In cases in which the right side of the heart is involved, scattered pulmonary infiltrates can sometimes be seen as a result of septic pulmonary emboli (Ellis et al, 1973).

2.3.2.4. Electrocardiography.

In uncomplicated infective endocarditis electrocardiographic findings are non-specific. Premature ventricular contractions are common during IE, occurring in about 20% (Snow and Cobbs, 1976). In case of aortic or mitral regurgitation of some duration, left ventricular hypertrophy can occur. As discussed earlier, varying degrees of heart block can occur (usually first degree but sometimes second or third degree), due, in most cases, to extension of the inflammatory process from the non-coronary cusp of the aortic valve into the proximal part of the ventricular septum. Bundle branch blocks may complicate myocardial abscesses or coronary artery emboli pointing to a poor prognosis (Roberts and Sommerville, 1969).

2.3.2.5. Myocardial imaging techniques.

Wiseman et al (1976) studied 11 patients with a clinical diagnosis of IE by scintillation scanning of the precordial region 2 to 7 days after the intravenous administration of 3 mCi of gallium-67 citrate. This isotope can concentrate in areas of acute inflammation. The gallium scans were interpreted as abnormal if a well defined zone of increased gallium activity was seen in the region of the cardiac blood pool. The scans were positive 3 to 8 days following injection in 7 patients. There are several disadvantages to this diagnostic approach in determining IE. There is an insufficient degree of resolution

to indicate the site of infection (the mass of involved tissue is relatively small), furthermore, it takes a lot of time (more than 3 days) to localize the radionuclide with a 36% incidence of false-negative results. Current efforts to develop new radioisotopes which might accumulate in areas of acute inflammation may increase the reliability of these studies in the future.

2.3.2.6. Echocardiography.

The first demonstration by (M-mode) echocardiography of valvular vegetations was reported in 1973 by Dillon et al, who identified characteristic thickened echoes on the mitral or aortic leaflets in 8 patients with autopsy or surgically proved valvular vegetations. The smallest vegetations detected in their study were 2 mm in diameter and the authors suggested that this might be the critical size required for echocardiographic identification. The most characteristic M-mode appearance of a vegetation is that of a non-uniform thickening of valve leaflet(s). The abnormal echoes producing the thickened valves are usually described as "shaggy". The sensitivity of the M-mode technique to detect vegetations in patients with IE is not high: Wann et al (1976) were able to visualize vegetations in 34% of the patients with IE, Young et al (1978) in 40%, Gura et al (1978) in 46% and Davis et al (1980) in 57%. All studies were done during active and proven infective endocarditis. This apparent lack of sensitivity can be attributed to a number of factors such as: vegetations may be smaller than the resolvant power of the equipment; pre-existent pathologic distortion of valvular anatomy may make the detection of superimposed vegetations very difficult; vegetations can be present in a "blind area" (for example, recesses of the valve or near the commissures); the timing of examination can be an important factor: vegetative lesions are rarely detected until 2 weeks after the onset of the symptoms (Stewart et al, 1980); vegetations need not always be present on valves in IE (they can be attached on the mural endocardium or when highly virulent micro-organisms cause the disease cardiac valves can be merely destroyed); and finally it is not always possible to

obtain a technically adequate echocardiogram. False positive examinations may also occur. For example, in patients with the mitral valve prolapse syndrome, thick shaggy diastolic echoes on the mitral leaflets closely resembling those seen with valvular vegetations can occur. Chandraratna and Langevin (1977) reviewed the echocardiograms of 85 patients with mitral valve prolapse. Abnormal diastolic echoes were seen in 34 patients (40%). Sometimes myxomas may be confused with vegetations (Dillon et al, 1973; Schweiger et al, 1980). Because of its wider field of view, two-dimensional echocardiography appears to be more suitable for the detection of vegetations; in addition it allows a better appreciation of the size and shape of a vegetation. It provides information about the spatial orientation of intracardiac surfaces thus making complications as paravalvular abscess (Mintz et al, 1979), sinus of Valsalva aneurysm (Schatz et al, 1981) or septal aneurysm (Fast and Moene, 1977) easier detectable. Two-dimensional studies are also useful in detecting ruptured chordae tendineae and flail aortic valve leaflets. M-mode echocardiography, however, can provide valuable information not readily available from two-dimensional studies: early closure of the mitral valve in the presence of acute aortic regurgitation (Botvinick et al, 1975); high frequency diastolic fluttering of the aortic valve suggesting disruption or destruction of the cusps (Lee et al, 1974); fine systolic mitral valve fluttering in patients with ruptured chordae tendineae (Meyer et al, 1977); in case of a Björk-Shiley mitral valve prosthesis the time interval from the aortic valve closure to the peak opening of the disc of the mitral valve (A2-MVO interval) can be measured and this interval is shortened in cases of high left atrial pressures as seen with paravalvular leakage or obstruction at the side of the prosthesis (Brodie et al, 1976). Sometimes, in case of significant paravalvular leakage, an unusual prosthetic disc "hump" may be present in early diastole (Bernal-Ramirez and Phillips, 1977). On the other hand, in difficult situations as prosthetic valve endocarditis and right-sided endocarditis two-dimensional echocardiography is generally superior in recogni-

zing abnormal intracardiac masses as demonstrated by Martin et al (1980): in 3 patients with aortic prostheses (2 bioprostheses and 1 caged ball prosthesis) two-dimensional echocardiography showed a definite mass on the valve, in the 2 bioprosthesis patients, and nearby the cage, in the third patient. M-mode studies indicated no abnormalities. Among 9 patients with a mitral bioprosthesis the two-dimensional study indicated a mass on the prosthesis in 8 patients, on the M-mode study in only 1 patient was there a definite mass on the valve to be seen, in 7 patients no abnormalities were found. In their total group of 43 patients with confirmed IE, in 47% vegetations were detected by M-mode technique and in 81% by two-dimensional echocardiography. However, as they stated, the thoroughness of the M-mode studies might have varied because a number of trainees in cardiology had primary responsibility for performing the M-mode studies, while three experienced echocardiographists consistently performed the two-dimensional studies. This difference might partly explain the differences in sensitivity obtained in the two types of study according to these authors. In this study two-dimensional echocardiography appeared to be superior to the M-mode technique. However, it is important to state that both methods should be used in conjunction to give the maximal amount of clinically useful information (Wann et al, 1979). Once the presence of vegetations is established by echocardiography, the patients appear to be at higher risk for embolic events, valvular disruption and congestive heart failure, than those without vegetations. This is clearly demonstrated in table 1 showing the combined figures from 5 groups of investigators. Nevertheless, none of these authors recommend valve replacement purely on the basis of echocardiographic demonstration of vegetations. A decision for surgery should be based on a combination of factors, especially the presence of refactory heart failure. In order to evaluate the influence of medical therapy on vegetation size and shape, Stewart et al (1980) performed serial echocardiographic examinations in 87 patients with proven IE. Evaluations were performed in the first, middle, and last third period of medical therapy. After

TABLE 1. Comparison of clinical findings (SE, CHF, surgical intervention or death) in patients with (+) and without (-) vegetations on echocardiography

	VEG.		SE	VEG.		CHF	VEG.		S and/or †
	+	-		+	-		+	-	
Stewart et al (1980)	38	40	14 / 4	38	40	14 / 1	38	40	15 / 4
Roy et al (1976)	22	10	12 / 2			?	22	10	11 / 4
Wann et al (1976)	19	43	4 / 0	19	43	19 / 12	19	43	17 / 0
Sheikh et al (1981)	12	5	7 / 1	12	5	11 / 1	12	5	11 / 2
Davis et al (1980)	17	13	8 / 2	17	13	14 / 6	17	13	17 / 4
Total	108	111	45 (=42%) / 9 (=8%)	86	101	58 (=67%) / 20 (=20%)	108	111	71 (=66%) / 14 (=13%)

VEG: vegetation, located on a left-sided cardiac valve
SE : systemic embolus
CHF: congestive heart failure
S and/or †: surgery and/or death
? : CHF not mentioned.

therapy, repeat echocardiographic evaluations were performed in intervals less than 1 month, 1-6 months and more than 6 months after therapy. Almost two-third of the echocardiographically detected vegetations remained stable with respect to size and shape throughout therapy and for as long as 36 months after bacteriologic cure. Complete disappearance was noted in 5 of the total of 110 lesions (5%), 3 during antimicrobial therapy, and 2 during convalescence. In 2 of these cases the lesions disappeared due to embolic events (each from the tricuspid valve during therapy). Vegetations increased in size in 10% during therapy, and in 13% in the convalescence period. They did not observe a development of vegetations

during therapy or convalescence in patients with negative initial studies. They found no relationship between change in size or shape of the lesion and efficacy of antibiotic treatment. In addition, classification of the vegetative lesions according to size was of little value in predicting complications: patients with small vegetations were as likely to develop complications as those with larger vegetations. Stafford et al (1979) obtained serial echocardiograms from 6 patients who had been treated with antibiotic drugs for IE. Three to six M-mode echocardiograms and one to six two-dimensional echocardiograms were obtained from each patient over a follow-up period averaging 50 weeks (range 10-108 weeks).
They concluded that vegetations became smaller and more echo-reflective with healing. This increase in reflection with healing was more readily appreciated on M-mode echocardiography and it was thought that this change in acoustic property of a vegetation was caused by hyalinization or calcification of the vegetation. Two-dimensional echocardiography was more helpful in judging the size and shape of the vegetations in their study. In a study of Sheikh et al (1981) patients with active IE involving the aortic valve were compared to those with active IE of the mitral valve. The aortic valve patients had a higher frequency of congestive heart failure (11 of 17 versus 12 of 29), a higher frequency of systemic emboli (8 of 17 versus 6 of 29), and a much higher frequency of valve replacement during the period of active infection (5 of 17 versus 4 of 29). They concluded that active IE involving the aortic valve is far more liable to produce complications, such as congestive heart failure and systemic emboli, to necessitate valve replacement and to cause death compared to the patients with mitral valve involvement.

2.3.2.7. Cardiac catheterization.
There is a considerable disagreement about the indication for cardiac catheterization prior to operative management. Authors who advocate cardiac catheterization pre-operatively are Mills et al (1977) and Welton et al (1979). The first authors per-

formed emergency cardiac catheterization and/or cineangiography pre-operatively in 19 patients with valvular insufficiency and severe heart failure. Angiography provided useful information which was not clinically apparent in 7 of these patients. One patient had a small fistula through the ventricular septum that was difficult to detect even at operation; one was admitted in cardiogenic shock with a non-specific murmur and had massive mitral regurgitation; in 3 patients aortic annular erosions were detected and 2 patients appeared to have double valve involvement. In all 19 patients supravalvular or left ventricular contrast injections were performed. There were 2 severe complications related to the contrast injection: one patient developed bradycardia, shock and death immediately following the injection; the other went into pulmonary edema. It is not quite clear from this study how many patients were catheterized in the active stage of the infective endocarditis and how often the aortic valve was passed by the catheter. In the study of Welton et al (1979) from the cardiology section of the Houston Veterans Medical Center, 35 catheterizations of the right- and left-side of the heart were performed during the active stage of infective endocarditis. Coronary arteriography was performed in only 13 patients, all with aortic valve involvement or with suspected co-existing coronary artery disease. Twenty-one valves were traversed by the catheter. On 15 valves vegetations were seen on echocardiography (unfortunately, the size of these vegetations was not mentioned in their report). The only complication was transient atrial fibrillation in one case, no embolization occurred. Clinically (physical findings, phonocardiography, echocardiography) unsuspected multiple valve involvement was diagnosed with cardiac catheterization in 7 patients. In 2 of them the hemodynamic consequences were severe enough to require replacement of the second valve. In 6 cases a valve ring abscess was diagnosed (2 abscesses involved the mitral annulus, 2 the aortic annulus, the remaining 2 abscesses were associated with aortic and mitral prosthetic valves). In 3 patients a left to right shunt was detected due to a ruptured sinus of Valsalva.

Although all shunts were suspected before catheterization on the basis of a new murmur, the place and degree of the shunt were unknown. In one patient a fistula visualized angiographically was initially not discovered at operation; knowledge of its presence led to a persistent search with eventual localization of a pinhole-sized opening on the ventricular side of the aortic cusp with a large tract to the right atrium. The opening was appropriately repaired. The importance of these pre-operative angiographic data was that the cardiac surgeon was able to plan his operative repair more securely: an extensive aortic ring abscess, for example, may necessitate resection of the involved segment, insertion of a dacron graft with a prosthetic valve and coronary arterial bypass grafting. Awareness of such difficulties before operation may save valuable time during cardiac surgery. They conclude that when cardiac catheterization is performed judiciously, it is a safe procedure and yields important and necessary information. Even when the clinical diagnosis seems apparent, cardiac catheterization should be performed in all patients with endocarditis in whom surgery is planned, unless the situation is so urgent that immediate surgical exploration is necessary. Opponents of this view are Snow and Cobbs (1976), Roy et al (1976), Gilbert et al (1976) and Stewart et al (1980). The first authors do not recommend cardiac catheterization pre-operatively because in their opinion the risks of the procedure (arrhythmias and dislodgement of vegetation) exceed the gain. The publications of the last 3 authors dealed primary with echocardiography. In the study of Roy et al (1976) 14 patients underwent surgery, 12 of them without prior catheterization; only one patient underwent coronary angiography and one right heart catheterization. They conclude that "echocardiography coupled with clinical findings gives one confidence in sending patients to surgery without catheterization; in presence of vegetations on echocardiography and a history of recent active disease it is believed that cardiac catheterization is particularly hazardous". In a two-dimensional echocardiography study of Gilbert et al (1976) a catheterization was performed (supravalvular aortography and

right heart catheterization, because a ventricular septum defect was suspected) in only one of the 6 patients undergoing surgery. In the other 5 patients the results of the echocardiography study, in combination with the clinical status, sufficed for patient management. In the study of Stewart et al (1980), 4 of the 12 patients underwent pre-operative catheterization. Stewart et al conclude that echocardiography is important for localization of lesions, evaluation of leaflet integrity and for estimation of left ventricular size and contractility. According to these authors, catheterization should be reserved for the patient in a hemodynamic stable state in whom there is a question of multiple valve involvement or intracardiac fistula.

2.4. Treatment

Before the introduction of antibiotics, the treatment of infective endocarditis was impossible. Various combinations of sulfonamides and other agents were used with little or no success. Mortality rate of these patients was virtually 100%. No other infectious disease appears to be as thoroughly dependent on appropriate use of effective antibiotics for survival as IE. The dense, avascular, fibrin-platelet vegetation appears to protect micro-organisms buried within from phagocytes and other host defense mechanisms. Effective antimicrobial therapy is possible today for most patients with IE.

2.4.1. General principles of therapy

Wilson et al (1980) summed up a number of general principles that should be adhered to in the treatment of all patients with IE.

1. Establish the microbiologic diagnosis, if possible before starting antibiotic therapy. In the subacute form of IE patients often have been ill for weeks or months, and there is usually no great urgency to initiate antibiotic therapy. In contrast, in patients with acute IE, the use of antibiotics should not be delayed until the results of blood cultures are known and therapy should be begun promptly after blood has been obtained for the initial set of blood cultures. The regimen should include a combination of antibiotics

effective against enterococci and penicillinase producing staphylococci.

2. Use bactericidal antibiotics and give them always parenterally as absorption from the gastrointestinal tract of orally administered antimicrobial agents may be unpredictable.
3. The dose of antibiotics should be sufficiently high to get a serum concentration at least 4 times greater than the concentration needed to kill the causative bacteria in vitro. This may be tested by making serial dilutions of the patient's serum inoculated with a standard inoculum of the patient's own bacteria. This so-called serum bactericidal test is very helpful, since it has been demonstrated that there may be a total lack of correlation between the usual in vitro antibiotic sensitivity tests and the results of therapy.
4. Within 48 hours after initiation of antibiotic therapy, blood cultures should be obtained to assess the efficacy of treatment. Persistently positive blood cultures in spite of apparently appropriate treatment could indicate myocardial, aortic root or distant abscesses, tolerance of bacteria to antimicrobial agents or error in administration or dosage of antimicrobial agents.
5. After antimicrobial therapy has been initiated the patients should be examined carefully, in order to identify the possible portal of entry of the causative agent. Patients with osteomyelitis, impacted teeth, or focal suppurative disease at other sites may need surgical or local therapy while the patient is receiving treatment for IE.
6. The patients should be examined daily, throughout their hospital course. Subtle changes in body weight, blood pressure, cardiac auscultatory findings, jugular venous distention and heart rate may presage abrupt hemodynamic decompensation. In case of heart failure cardiac surgery shoud be considered.
7. During therapy patients should remain relatively inactive to minimise cardiac work and valve damage. Some mobility may be permitted, however, to the patient with minimal valve involvement and a rapid response to treatment.
8. IE is a potentially lethal disease and physicians should

resist the temptation to compromise on the duration and means of administration of therapy or to switch to less effective antimicrobial agents. After initiation of therapy, most patients will experience a dramatic improvement in general well-being and disappearance of fever. These improvements must not be interpreted as an indication that the antimicrobial therapy may be switched to orally administered agents or that the length of treatment may be shortened.

9. In the case of drug hypersensitivity alternative antibiotic medication can be used: for example, cephalosporins or vancomycin. (Controlling the hypersensitivity reaction by adding steroids may be dangerous: the one patient with benzylpenicillin allergy treated with steroids by Fleming and Newsom, 1980, suffered a large brain embolus. Since then these authors prefer to use the before mentioned alternative antibiotics.)
10. Before hospital dismissal, the patient should receive adequate instructions regarding profylactic measures for IE.
11. Follow-up blood cultures should be obtained at 1 and 2 months after completion of antimicrobial therapy. (Van Furth (1981) starts blood culturing on the fourth day after drug withdrawal as follows: 3 cultures on each of the first 2 days, one culture 2 and 4 weeks later; then one every 4 weeks for the next 6 months.) If all these cultures are negative, the endocardium or intima must be regarded as free of infection.

2.4.2. Cardiac surgery

2.4.2.1. History.

Cardiac surgery plays an important supplementary role to antibiotics in the management of complications of IE. Kay and his colleagues (1961) successfully cured a patient with candida albicans endocarditis which had not responded to amphotericin-B, by removal of bulky vegetations of a tricuspid valve leaflet (combined with closure of a ventricular septal defect). In 1964 Yeh et al reported six cases in which operation was performed after a complete antibiotic course and because of severe heart failure due to aortic regurgitation. In 5 patients the valves

were repaired by sutures; in 1 patient, a Starr-Edwards prosthesis was implanted. In 1965 Wallace et al described cure of active aortic valve endocarditis with Klebsiella (after prolonged ineffective intermittent antimicrobial therapy) by valve excision and replacement with a mechanical prosthesis. Subsequently, the strategy of open heart surgery in the management of IE has been pursued in numerous centers. However, as is often the case with progress in medicine, the development of new methods of management, while solving one set of problems, frequently creates new ones. Rapaport pointed out in an editorial in Circulation (1978) that surgery to replace a damaged valve incurs the risk of endocarditis. The irony lies in the fact that prosthetic valve replacement is increasingly being used therapeutically to manage prosthetic valve infection.

2.4.2.2. Indications.

The indications for cardiac surgery are:

1. Heart failure. This constitutes the major indication for surgery. The degree of hemodynamic impairment and the patient's response to conventional measures of therapy usually dictate when surgery is to be done. It is generally agreed that severe heart failure associated with valvular incompetence is an indication for operation. When mild heart failure occurs during IE (symptoms of left heart failure disappearing soon after digitalis and/or diuretics) operation also has to be done according to Griffin et al (1972). This conclusion is based on their finding that 7 out of 11 patients with aortic regurgitation and mild heart failure suddenly died. Four of them had myocardial infarctions at autopsy. Contrary to this observation, Mills et al (1974) noted a 7% mortality rate: two out of 29 patients with mild heart failure and aortic regurgitation died suddenly. Death appeared to be related to acute perforation followed by rapid deterioration over the ensuing few hours. Most authors advise a careful observation of such patients and surgical intervention at the first sign that heart failure returns,

regardless of the length of prior antibiotic therapy. Delaying operation in the hope of "stabilizing" the patient with moderate or severe heart failure, will increase perioperative mortality. The hemodynamic status must be the determining factor leading to surgical intervention, irrespetive of the duration of antibiotic therapy (Okies et al, 1973; Mills et al, 1974; Parrot et al, 1976; Richardson et al, 1978).

2. Persistent infection. When micro-organisms are situated on fibrocalcific valves, prostheses (especially when dehisced) or in abscesses they are relatively isolated from host defenses with resultant persistent infection. Another cause can be that some organisms, for example gram-negative bacteria or fungi, are not very susceptible to the drug administered. Candida albicans endocarditis is a classic example of an organism requiring surgical debridement since in most of these cases amphotericin B or 5-fluorocytosin alone or in combination has failed to produce cure. In all cases of persistent infection during effective antibiotic therapy sites of occult abscess, such as in liver, spleen, kidney, brain, should be sought for. The CT-scan may be especially useful for delineation of abscesses in brain or abdomen. Other disorders which may mimic persistent endocarditis may be: toxic or hypersensitivity reactions to antibiotic drugs, concomitant disease such as acute rheumatic fever or disseminated lupus erythematosis, and septic phlebitis at the site of administration of antibiotic therapy (Cobbs and Livingston, 1981).
3. Emboli. Systemic emboli can cause difficulties: a) by occlusion of major vessels; b) by serving as a nidus of infection with formation of mycotic aneurysms or secondary abscesses (Buchbinder and Roberts, 1972). If a systemic embolus occurs Pankey (1979) advises that an echocardiogram should be made and when a residual valvular vegetation is seen, surgical intervention is advised. If no vegetations, or only small ones, are identified and no additional emboli occur, medical therapy is advisable. This rule is also

applied to patients with right-sided endocarditis and pulmonary septic emboli.

4. Progression of intracardiac infection.
   Atrioventricular conduction disturbances are most often the result of burrowing infections in the interventricular septum. The infection may lead to intracardiac fistulae, which can precipitate or aggravate congestive failure. These burrowing myocardial infections are generally associated with highly virulent organisms, such as staphylococcus aureus, and are difficult to treat medically (Okies and Starr, 1978).
5. Controversial indications. Richardson et al (1978) recommend early surgery in patients with staphylococcus aureus infection because of the poor prognosis. In their analysis of surgical and non-surgical treatment of active native valve endocarditis in 135 patients over a 10 year period they saw heart failure, annular and myocardial abscesses, heart block, and coronary embolism most frequently with staphylococcus endocarditis. Seven of the 16 medically treated staphylococcus aureus patients died (44%), on the other hand 3 of the 23 staphylococcus aureus patients who were surgically treated died (13%). Their conclusion that patients with staphylococcal endocarditis, regardless of hemodynamic state, should undergo early valve replacement is believed to be premature by Rapaport in an editorial comment in Circulation (1978). In his judgement medical therapy should be initially utilized in patients who are hemodynamically stable. Of course such patients should be followed extremely closely and if evidence of hemodynamic deterioration appears, they should be considered for urgent or emergency valve replacement.

Stinson (1979) considers progressively severe renal failure due to immunecomplex glomerulonephritis as another indication for cardiac surgery. However, the occurrence of renal failure during antibiotic therapy may be the result of complications of this therapy: acute interstitial nephritis, for instance, can be caused by treatment with penicillins; acute tubular necrosis,

by aminoglycosides therapy (Wilson et al, 1978). These authors advise intermittent hemodialysis when renal insufficiency is severe (they do not mention cardiac surgery at all) and renal biopsy if etiology of renal failure cannot be defined clinically.

2.4.2.3. Mortality rate of operative therapy versus medical therapy.

Before antibiotics were available 97% of patients with IE died when severe congestive heart failure was present. When moderate or severe heart failure developed during the course of the disease under antibiotic coverage, the mortality rate was 79% to 93% (Kerr, 1955; Snow and Cobbs, 1976). Reported surgical (hospital) mortality rates range from 14% (Richardson et al, 1978) to 37% (Young et al, 1978). In a review of 286 cases of left-sided IE treated surgically, published by Jung et al in 1975, the early mortality rate in the patients with "active" IE was 30%, late mortality was 7%. For the "healed" patients (operated after completion of antibiotic course) these figures were 12% and 11%. The mortality rate, both early and late, for the whole series was 31%. When patients were operated upon under urgent circumstances because of severe congestive heart failure the mortality was 34%, whereas elective operations carried a mortality rate of 15%. Richardson et al (1978) reported a low overall mortality rate (14%) in 81 surgically treated patients with active IE. However, 60% of the patients were operated in a favorable hemodynamic state (absent or mild heart failure). When patients were in a bad pre-operative hemodynamic state (severe left-sided heart failure), mortality was high (4 out of 12 patients = 33%).
Young et al (1978) reported a surgical mortality rate of 37% (11 out of 32 patients with active IE). All deaths occurred in patients moribund prior to surgery. The authors of these three studies concluded that operative mortality for patients with active IE is directly related to the severity of congestive heart failure and to the patient's general medical condition pre-operatively.

2.4.3. Surgical techniques and problems

The goals of operation are to remove all infected and necrotic tissue, restore valvular function by valve replacement, and correct additional defects: such as, septal perforations, aortic aneurysms or fistulas. Heart block can occur as a result of burrowing infection or from debridement and repair, making pacemaker insertion (preferably using epicardial wires), necessary (Stinson, 1979). Special technical problems arise in cases of perivalvular infection in which annular abscesses spread to the aortic wall or into the ventricular septum. Especially in patients with prosthetic valve endocarditis, annular abscess (i.e. infection of the tissue at the interface between the seat of the prosthesis and the endocardium of the patient) is a common complication (Dismukes, 1981). Different situations can be expected after excision of the necrotic material or removal of infected prosthetic valve:

a) the aortic annulus is only moderately affected (fig. 1a). A prosthetic valve can be inserted in place. Special measures may be required in order to reinforce suture-lines and minimize the occurrence of postoperative periprosthetic leaks. In the series of Stinson (1979), this was accomplished by bolstering mattress sutures with synthetic material. In the case of aortic valve prosthesis implantation sutures were inserted from outside the aorta around the entire circumference of the aortic annulus; if necessary, the proximal pulmonary artery or right ventricular outflow tract were opened and sutures were passed from within these structures to enter the aorta in the region of the left and right coronary cusps.
b) the aortic annulus is extensively affected, but the orifices of the coronary arteries are not included (fig. 1b). In that case reconstruction of the annular (and sub-annular) region using a Dacron or pericard patch has to be done with subsequent placement of a prosthetic valve (fig. 1c).
c) the aortic annulus is extensively affected with extension of the infection into the region of the orifices of the coronary

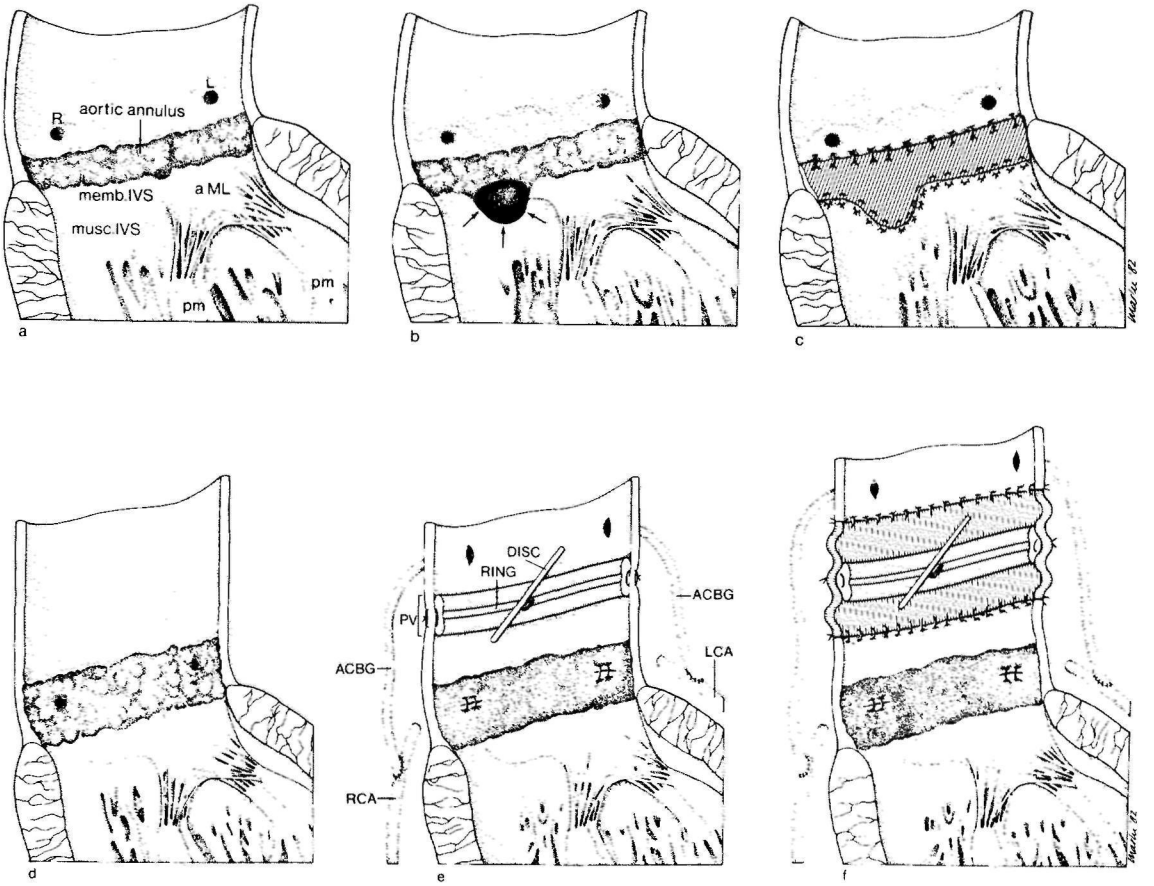


Figure 1. Drawings of lesions, sometimes encountered at surgery after excision of aortic valves or removal of infected prosthetic valves, necessitating special corrective surgical techniques. See text for details.

a. the aortic annulus is only moderately affected.
b. the aortic annulus is extensively affected with perforation of the ventricular septum (arrows).
c. reconstruction of the annular and subannular region, using a Dacron patch.
d. the aortic annulus is extensively affected with extension of infection into regio of orifices of coronary arteries.
e. implantation of prosthetic valve in ascending aorta with closure of orifices of the coronary arteries and insertion of aorto-coronary bypass grafts.
f. interposition of a prosthetic valve-containing Dacron graft in the midportion of the ascending aorta.

Abbreviations: memb. IVS = membranous part of the interventricular septum, musc. IVS = muscular part of the interventricular septum, aML = anterior mitral leaflet, pm= papillary muscles, R = orifice of right coronary artery, L = orifice of left coronary artery, RCA = right coronary artery, LCA = left coronary artery, ACBG = aortocoronary bypass graft, PV = prosthetic valve.

arteries (fig. 1d). In that case a prosthetic valve can be placed in the ascending aorta (fig. 1e) or - a slightly different and easier technique - a Dacron graft containing a prosthetic valve is interposed between the two ends of the intersected ascending aorta (fig. 1f). Thus, the coronary orifices have a subvalvular position; this necessitates ligation of the right and left main coronary arteries at their origins, and aortocoronary bypass grafting with proximal attachments of the grafts above the prosthetic valve (Danielson, 1974; Stinson, 1979; Ganqjbakhch, 1981). Another fundamentally different technique is the insertion of a valvular dacrontube from the apex of the left ventricle to the abdominal aorta with closure of the original (debrided) aortic orifice.

Aortocoronary bypass grafting of course is necessary (fig. 2). This technique, originally described in cases of con-

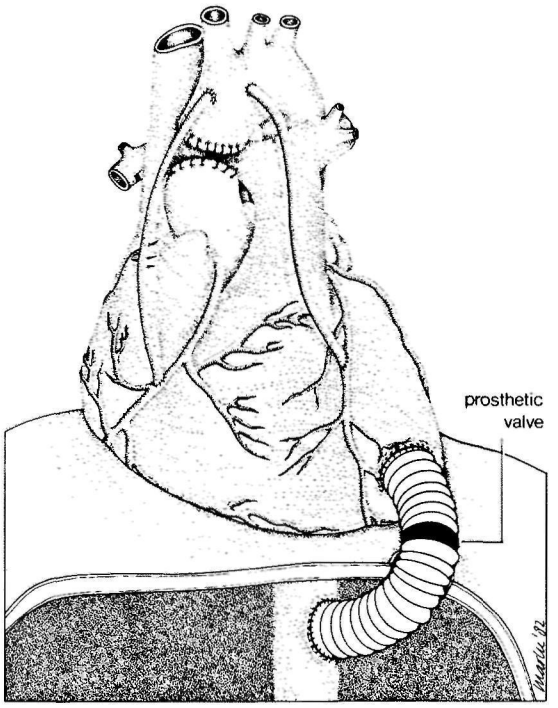


Figure 2. Apicoaortic bypass with a prosthetic valve-containing Dacron graft.
The conduit passes from the left ventricular apex through the left leaf of the diaphragm to the supraceliac abdominal aorta. The aorta is closed just above the (debrided) aortic orifice, necessitating aortocoronary bypass grafting.

genital hypoplastic aortic annulus, has been successfully performed in a few patients with IE (Gandjbakhch et al, 1981).

What is the prosthesis of choice in active endocarditis? Rossiter et al, (1978) reviewed their experience with prosthetic valve endocarditis (PVE): 2184 patients underwent prosthetic valve replacement at Stanford University Medical Center from 1963 to 1977; 837 patients received Hancock gluteraldehyde preserved porcine heterograft valves and 1347 patients received mechanical Starr-Edwards valves. PVE occurred in 51 patients, early in 9 (< 2 months postoperatively) and late in 42 (> 2 months postoperatively). The incidence of PVE for the 14 year period was 1.9% (16/837) for the Hancock-group and 2.6% (35/1347) for the mechanical valve group. The difference is not significant. However, heterograft valves, once infected, were more easily cured by antimicrobial therapy than infected mechanical valves. This might be explained as follows: in the case of mechanical prosthesis endocarditis, infection always occurs in tissue adjacent to the sewing ring (Dismukes, 1981), often leading to formation of annular abscesses. Micro-organisms in these abscesses are relatively isolated from host defenses and cure with antimicrobial therapy is very unlikely. As with native heart valves, endocarditis of heterograft valves usually occurs first on the leaflet tissue. If detected and treated during this stage infection might be more easily eradicated. The same observation has been made by Magilligan et al, (1977). In their series of 373 patients with Hancock porcine heterograft valves they reported 11 cases of PVE. Blood cultures in 10 patients treated with antibiotics promptly became negative (the eleventh patient had candida on the porcine valve, this was discovered unexpectedly on postmortem examination).

In an editorial in Annals of Thoracic Surgery (1981) Scott advises insertion of bioprosthetic valves, rather than mechanical valves, at sites where active infection is present. It is suggested that the sewing ring of the bioprostheses is more resistent to infection than the sewing ring of the mechanical valves because it has had prolonged fixation with gluteraldehyde.

According to Huysmans, (1981) a mechanical prosthesis should be used in operations for active IE; such a type of prosthesis will not easily be impaired in its function by a persistent infection and is easier to handle if a re-operation should be necessary.
As Scott (1981) states: "surgeons have a natural preference for prostheses that have proved to be most satisfactory in their own experience".

3.1. METHODS

3.1.1. Patient population

All operation reports from adult patients undergoing open heart surgery in the St. Radboud Hospital since 1972 were reviewed. In 57 patients the cardiac surgeon used the term "endocarditis" in the clinical summary (preceding the operation report) or the words "vegetations", "verrucae" in his operation report. The medical records of these patients were carefully reviewed, records of referring hospitals were also reviewed when available. The diagnosis of IE was based on criteria of Vogler et al (1962). By using Vogler's criteria 11 patients were excluded because of insufficient evidence of endocarditis. So 46 of the 57 patients were accepted for this study because one or both of the following two criteria were present:

1. isolation of micro-organisms from 2 or more subsequent blood cultures in combination with at least 3 of the following clinical features:
   a) fever
   b) a new or changing heart murmur
   c) "peripheral stigmata": petechiae, subungual ("splinter") hemorrhages occurring during patient-observation, Osler nodes, Janeway lesions, ocular signs, clubbing of fingers and/or toes, splenomegaly.
   d) laboratory abnormalities (anemia, elevated ESR, normal or elevated leukocyte count with "shift to the left")
2. sterile blood cultures with 3 or more of the above mentioned clinical features in combination with characteristic macroscopic or microscopic abnormalities of the surgical specimens.

Endocarditis involving previously normal or abnormal heart valves was called "native valve endocarditis"; infective involvement of previously inserted prostheses: "prosthetic valve endocarditis". Prosthetic valve endocarditis was called early, when endocarditis occurred within 2 months after valve implan-

tation; and late, when it occurred 2 months or longer after valve implantation. Cases were classified clinically into "active" or "healed" groups, according to whether operation was done during antibiotic treatment ("active"), respectively after completion of a course of antibiotic therapy ("healed"). This distinction does not necessarily imply that the infective process itself is/was really active or inactive. Patients were furthermore categorized as having normal cardiac function, mild, moderate, and severe congestive heart failure. The classification of the heart failure was based on response to therapy as reported by Griffin et al (1972).

Mild heart failure was characterized by dyspnea with activity (class 2-3 New York Heart Association), moist rales at the lung bases, a ventricular gallop sound on physical examination and increased pulmonary venous vascularity ("redistribution") on chest X-ray. These symptoms and findings responded well to treatment with a low sodium diet or diuretics alone or to any of the following combinations: digitalis with a low sodium diet or digitalis with low doses of diuretics maximal two or 3 times a week.

Moderate heart failure was characterized by similar symptoms and findings which responded to a low sodium diet, digitalis, and/or diuretics in higher doses and more frequently.

Severe heart failure was characterized by dyspnea at rest (class 4 New York Heart Association), rales higher than halfway up the lungfields, gallop rhythm, and pulmonary interstitial or alveolar edema on chest X-ray. These symptoms and findings did not respond to a strict low salt diet, administration of digitalis and daily diuretics.

The time of development of various degrees of heart failure was determined as accurately as possible from the patient's medical record in combination with revision of chest X-rays. Only the classification immediately prior to surgery will be used in this study.

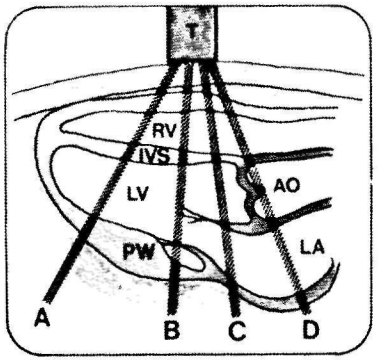


Figure 3a. Transducer positions for examining different areas of the heart.

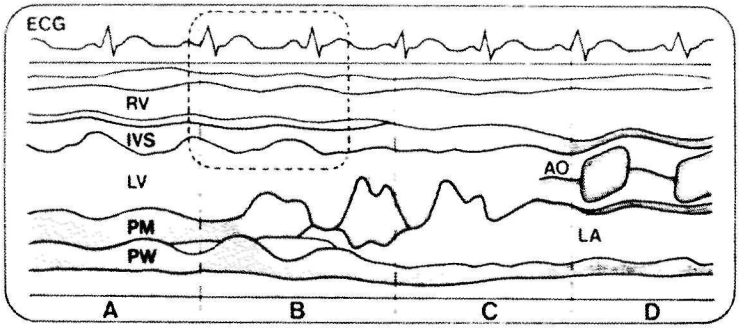


Figure 3b. M-mode echocardiographic recording as the transducer is directed from the apex (position A) to the base of the heart (position D). The areas between the dotted lines correspond to the transducer position as depicted in figure 3a.

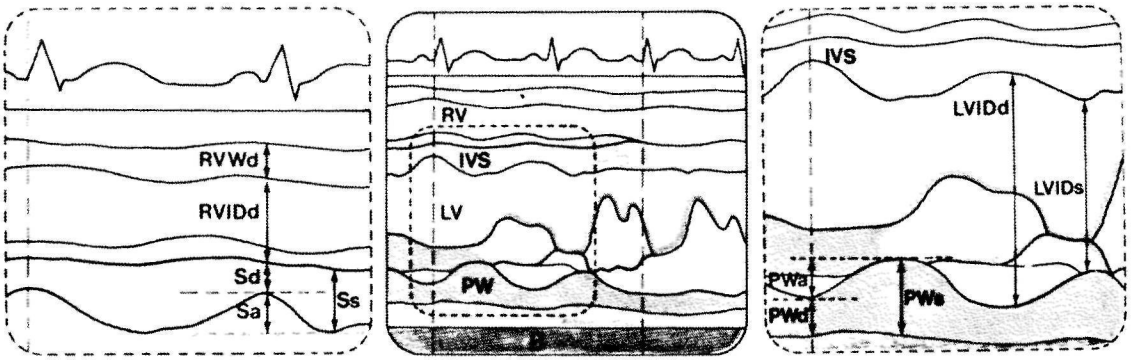


Figure 4. Ventricular measurements (transducer position B). RVIDd = RV; LVIDd = LVEDD; LVIDs = LVESD; Sd = IVSth; Sa = IVSexc; PWd = LVPWth; PWa = LVPWexc: see text.

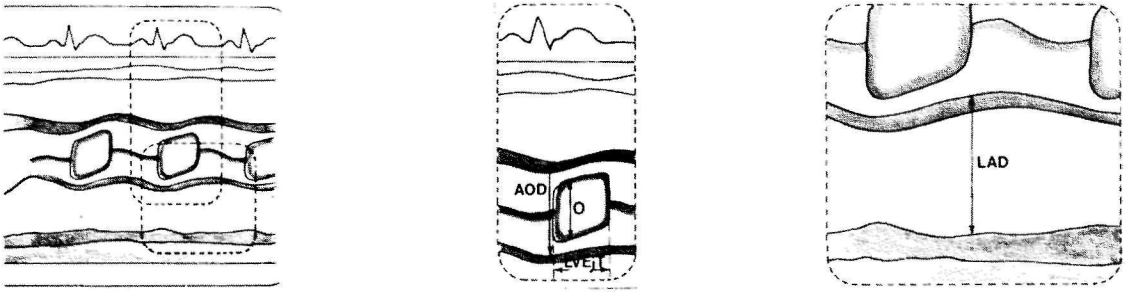


Figure 5. Measurements at the base of the heart (transducer position D). AOD = Ao; LAD = LA: see text. O = systolic separation of aortic valve leaflets.

3.1.2. Diagnostic aids

Electrocardiograms (12-lead system) immediately prior to operation were compared with those recorded 2 weeks after operation with emphasis on occurrence of left ventricular hypertrophy (LVH) using the pointscore system of Romhilt-Estes ("Estes-score" of > 5 points is read as LVH, 4 points as probable LVH. The criteria and their point-score were as follows: 3 points were given if anyone of the following was present:
a) largest R or S wave in the limb leads $\geq$ 20 mm; b) S wave in V_1 or V_2 $\geq$ 30 mm; c) R wave in V_5 or V_6 $\geq$ 30 mm; 3 points (with digitalis 1 point) if typical ST-T pattern of left ventricular strain was present; 3 points if the terminal negativity of the P wave in V_1 was 1 mm or more in depth with a duration of 0.04 second or more; 2 points if left axis deviation of -30^{o} or more was present in the frontal plane; 1 point when the QRS-duration was $\geq$ 0.09 second; 1 point when the intrinsicoid deflection in V_5 or V_6 was equal to or greater than 0.05 second.).
Chest X-rays of all patients were reviewed including those from the referring hospitals. The heart-lung ratios were measured only when X-rays were made with the patient in standing position; "bed-X-rays" were excluded. In every patient particular attention was given to changes in the cardiac configuration and lung vessels during the episode of infective endocarditis.
Echocardiography was done in all 31 patients operated upon since June, 1976. In the early period, M-mode echocardiograms were performed only with the Echocardiovisor 01 (Organon Teknika). Since April, 1978, in addition, examinations were performed with the Smith-Kline ultrasonoscope. We always used a 2.25 megaHertz ultrasound transducer focused at 7.5 cm; the examinations were recorded on light-sensitive paper using a Honeywell stripchart recorder. Patients were examined in the supine or left lateral position with the ultrasound transducer placed in the third or fourth intercostal space as close as possible to the left sternal border. The transducer (and the ultrasonic beam) was swept in a sector between the apex (position A, fig. 3) and the base of the heart (position D, fig. 3).

Paperspeed was 25 mm per second, in general, in some patients, 50 mm per second. From the M-mode tracings the following measurements were made (as recommended by Roelandt, 1977; Sahn et al, 1978) and are shown in figures 4 and 5.

a) Right ventricular dimension (RVIDd, measured at the onset of the first deflection of the QRS-complex of the ECG): distance between the right-sided endocardium of the anterior wall of the right ventricle and the right-sided endocardium of the interventricular septum.

b) Left ventricular end-diastolic dimension (LVEDD, measured at the onset of the first deflection of the QRS-complex of the ECG): distance between the left ventricular posterior wall endocardium and the left-sided endocardium of the interventricular septum.

c) Left ventricular end-systolic dimension (LVESD): the distance between left ventricular posterior wall endocardium at its most anterior position and left-sided endocardium of the interventricular septum.

d) Left ventricular posterior wall thickness (LVPWth): the endocardial-epicardial distance at the first deflection of the QRS-complex of the ECG.

e) Interventricular septal thickness (IVSth): from left-sided endocardium to right-sided endocardium at the first deflection of the QRS-complex of the ECG.

f) Amplitude of left ventricular posterior wall systolic movement (LVPWexc): vertical distance between posterior wall endocardium at end-diastole and end-systole. Amplitude of interventricular septal systolic movement (IVSexc): vertical distance between left-sided endocardium of the septum at end-diastole and end-systole. The left ventricular dimensions, posterior wall thickness/movement and septal thickness/movement were measured on the echocardiogram when both mitral leaflets could just be seen approaching the papillary muscles. In addition, the % fractional shortening (FS) was measured as an echocardiographic index of left ventricular function as follows: LVEDD-LVESD/LVEDD.

g) Aortic root (Ao) measured from the outer margin of the

anterior aortic wall to the anterior margin of the posterior aortic wall at end-diastole.

h) Left atrial dimension (LA): from the anterior margin of the posterior aortic wall to the anterior margin of the left atrial posterior wall at end-ventricular systole.

i) Ratio of left atrial dimension to aortic root dimension $(\frac{LA}{Ao})$.

In most patients, two-dimensional echocardiographic studies were performed as well, initially using the multi-element transducer (Organon Teknika), later the Ekosektor I (Smith Kline Instruments). The scanner probe of this last instrument contains a 2.25 MHz transducer that is mechanically driven through either a 30^{o} or 82^{o} sector arc. The last seven patients in our series were also examined with a wide angle (78^{o}) electronic phased array sector scanner (Toshiba SSH-10A). Complete 2-dimensional studies included the long-axis view, the transverse (short-axis) view and the apical (four-chamber) view. In general, only long axis views could be obtained with the Organon transducer. Most 2-dimensional echocardiograms were recorded for later analysis on videotape.

Echocardiographic criteria

a) Vegetation: presence of an irregular, shaggy mass of echoes creating a non-uniform thickening in several areas of a leaflet and not preventing the valvular motion (Dillon et at, 1973; fig. 6A,B).

b) Flail (disrupted) aortic leaflet: a high-frequency diastolic fluttering of (part of) the valve with echoes extending from aortic valve into the left ventricular outflow tract during diastole (Wray, 1975).

c) Flail mitral leaflet (ruptured chordae tendineae): fine systolic mitral leaflet fluttering (for detection of this finding, the paperspeed must be set on 50 mm per second) and chaotic diastolic fluttering of one or both leaflets (Meyer et al, 1977; Duchak et al, 1972). With 2-dimensional echocardiography, the diagnosis was made when the normal

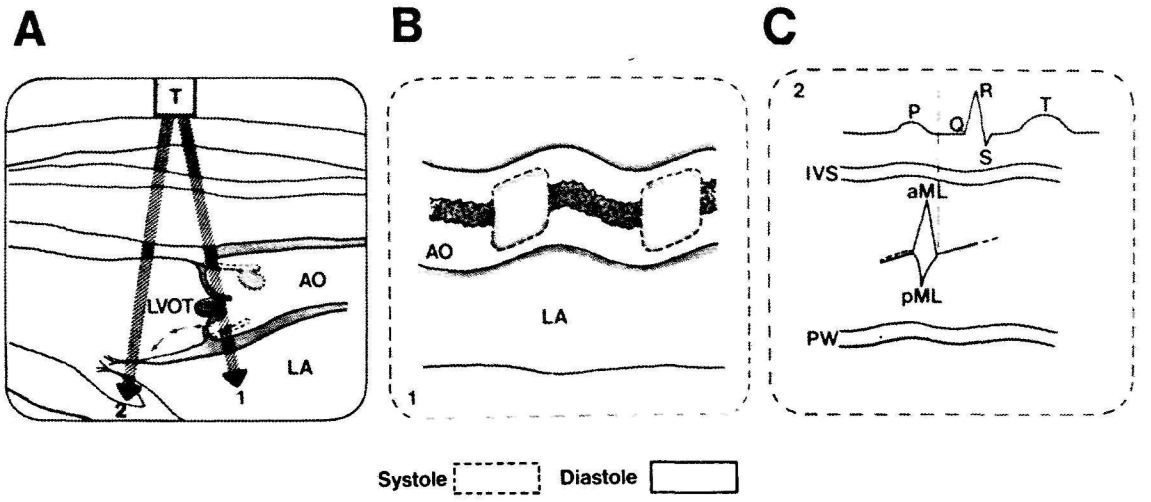


Figure 6. Aortic valve with vegetation attached to the anterior leaflet, and perforation of the other valve leaflet.
A. Transducer position 1. As a result of the direction of the ultrasonic beam, the vegetation is not recorded during systole (dotted line). During diastole the vegetation comes into the ultrasonic beam. B. During systole (dotted line), the normal "boxlike" configuration of the aortic valve leaflets is seen. During diastole a dense band of echoes occupies a mid-aortic position. C. Transducer position 2. Because of perforation of one of the aortic valve leaflets, the regurgitant blood into the left ventricle (small arrows, fig. 6A) elevates the left ventricle diastolic pressure beyond that of the left atrial pressure and the mitral valve closes early (broken vertical line indicates mitral valve closure point in relation to QRS complex of the ECG).

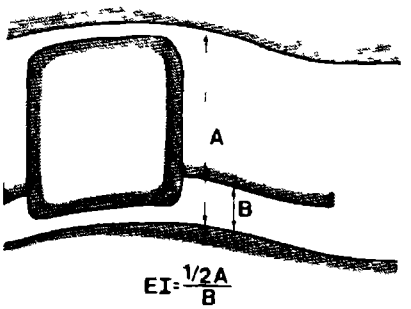
systolic coaptation point of both leaflets was lost with abnormal motion of the involved leaflets beyond the line of valve closure into the left atrium (Mintz et al, 1978).

d) Early closure of the mitral valve: coaptation of the anterior and posterior leaflets before the onset of the QRS-complex in the absence of prolonged PR-interval (Botvinick, 1975; fig. 6C).

e) Hyperkinetic wall motion: exaggerated systolic septal motion (> 8 mm) together with increased systolic amplitude (> 15 mm) of the left ventricular posterior wall (Roelandt, 1977).

f) Mitral valve prolapse: a posterior systolic motion of the mitral valve more than 2 mm from a line joining the C- and D-points (Fast, 1980; the C-point is the point where the anterior and posterior mitral valve leaflets come together at end-diastole; D is the point of abrupt anterior motion of the anterior mitral leaflet and posterior motion of the posterior mitral leaflet at the onset of diastolic valve opening). Mitral valve prolapse was diagnosed with two-dimensional echocardiography when one or both mitral leaflets showed a motion toward the left atrium passing the level of the mitral valve ring in systole with intact point of mitral valve leaflet coaptation (Mintz et al, 1978).

g) Bicuspid aortic valve. This diagnosis was made, in most cases, on the revised M-mode echocardiograms. The diastolic closure line lies eccentrically within the aorta. This eccentricity was quantitated as an "eccentricity index" (E.I.) as proposed by Nanda and coworkers (1974).



This E.I. is measured by dividing half the aorta dimension (A) through the smallest diastolic distance from the valve closure-line to the nearest wall of the aorta (B). The measurements were taken just after aortic valve closure (fig. 7). An E.I. of 1.3 or greater means a bicuspid aortic valve.

Figure 7. See text.

(The diagrammatic presentations of the echocardiograms (figures 3-7) are from Daniels, O., Drayer, J.I.M., Fast, J.H. and van Leeuwen, K.: Introductie tot echocardiografie, Bunge, Utrecht, 1980).

Invasive methods

In most patients a catheterization of the right side of the heart was done with the following measurements (normal values

between brackets): Pulmonary capillary wedge mean pressure (4-15 mmHg), systolic pulmonary arterial pressure (< 20 mmHg), right atrial mean pressure (1-5 mmHg); cardiac output was measured by the thermodilution technique and/or by the Fick method (3-5 l/min), cardiac index (= cardiac output/m^2 body-surface area, 2.5-4 l/min/m^2). These measurements were made with the Swan-Ganz catheter. In addition, blood samples were taken from the different heart compartments for measurement of oxygen saturation. When left heart catheterization was performed, the aortic systolic pressure was measured (100-150 mmHg) and sometimes, the left ventricular end-diastolic pressure (0-15 mmHg). These measurements were made prior to angiography with pigtail catheters. When contrast angiography was performed the cineangiograms were studied with regard to the following features:

1. the presence and degree of aortic or mitral regurgitation
2. morphological abnormalities of the valves and adjacent structures
3. the occurrence of intracardiac fistulas
4. the wall motion of the left ventricle
5. the anatomy of the coronary arteries.

To quantitate aortic and mitral regurgitation angiocardiographically the following criteria proposed by Sellers et al (1964) are followed:

1. Aortic regurgitation. +: only regurgitant jet, ++: regurgitant jet and faint opacification of the left ventricle, +++: dense opacification of the left ventricle, ++++: left ventricular opacification more dense than the aortic.
2. Mitral regurgitation. +: regurgitant jet with minimal opacification of the left atrium which clears rapidly, ++: regurgitant jet with moderate opacification of the left atrium which clears rapidly, +++: no jet, the left atrial opacification is as intense as that of left ventricle and aorta on the late films. Usually the left atrium is enlarged, ++++: the left atrial opacification is more intense than that of left ventricle and aorta, and the intense opacification persists throughout the entire film. Dilatation of

left ventricle and marked left atrial enlargement.

3.1.3. Operative procedures

Cardiac operations were performed by (different) cardiac surgeons of the department of Thoracic- Cardiac- and Vascular Surgery (Head: Prof.Dr. L.K. Lacquet). The surgical technique was as follows. After a median sternotomy, cardiopulmonary bypass was carried out with the Temptrol or BOS bubble oxygenator. Venous drainage was placed through the right atrium in the venae cavae and aterial inflow into the ascending aorta (in case of re-operation in a common femoral artery). The blood was cooled to 20°C until the rectal temperature of the patient reached 29°C. The ascending aorta was cross-clamped and the blood temperature was raised to maintain the rectal temperature. Before 1978, the myocardium was protected by coronary perfusion with oxygenated blood; in the case of aortic valve replacement coronary perfusion and aortic cross-clamping were continuous while the heart was beating, whereas during mitral valve replacement coronary perfusion and aortic cross-clamping were intermittent. Since 1978, myocardial protection was achieved through repeated injection of cardioplegic solution$^{\Delta}$ at 4°C in the aortic root or in the coronary ostia. These injections maintain electrical standstill and a myocardial temperature of 13-18°C.
The pericardial cavity was concomitantly irrigated with cold Ringer solution (according to Shumway). In the case of aortic involvement, the aortic valve was approached through an oblique aortotomy. In the case of mitral involvement, the mitral valve was approached by a longitudinal left atrial incision. Sometimes the transverse biatrial transseptal incision described by Dubost was used, especially in re-operations. The right atrium approach and longitudinal septal incision was preferred

$^{\Delta}$ content of 1 liter cardioplegic solution: 60 g hydrolysat, 36,44 g mannitol, 1,982 g glucose, 721 mg Mg asparat, 1,1 g procaine HCl, 74 mg Ca Cl_2, 1,461 g NaCl, 373 mg KCl.

in case of concomitant tricuspid valve regurgitation, thus making annuloplasty or valve replacement possible.
In case of right-sided endocarditis the surgical approach depended upon the site of the (presumed) lesions. When pulmonary valve-, right ventricular outflow tract- or tricuspid valve-pathology was present, respectively the pulmonary trunk, the ouflow tract of the right ventricle, or right atrium was opened. In patients with active infection or recently healed infections areas of necrotic tissue were debrided as thoroughly as possible, including the interior of perivalvular abscess cavities. The excised material (native valves, prosthetic valves, vegetations, subvalvular structures) was sent to the department of bacteriology (Head: Prof.Dr. G. van der Ploeg) and/or to the department of pathology (Head: Prof.Dr. G.P. Vooys). In patients with active infection the operative field was irrigated with antibiotic solutions. After valve excision, a prosthetic valve was implanted. Two basic types of heart valve substitutes were used: a Björk-Shiley tilting disc valve with pyrolite occluder and cloth-covered sewing ring or a gluteraldehyde preserved bioprosthetic valve combining a cloth-covered supporting strut with heterologous tissue. In the case of the Carpentier-Edwards or Hancock valve, this tissue consisted of porcine valves; in case of the Ionescu-Shiley valve, the leaflets were made of bovine pericardium. To minimize the occurrence of postoperative periprosthetic leaks, especially in patients with valve annulus destruction bolstering mattress sutures with dacron were used. After this the heart was closed; strict precautions were taken to avoid air embolization when the aortic clamp was released and the cardiac action resumed, either spontaneously or after electric defibrillation. Temporary epicardial electrodes were inserted on the ventricular anterior wall and the sternotomy was closed, leaving behind pericardial, mediastinal, and eventually pleural drains. During the perioperative period, cephalotin was used as the prophylactic antibiotic drug of choice due to its effectiveness in combating staphylococci. One gram was given intravenously shortly before operation, and then every 1½ hour during operation. The same dose was repeated every 4 hr

after operation until 48 hr after operation. In the "active group" of patients antibiotic therapy for a longer period of time was individually given according to pre-operative duration of treatment, the results of intra-operative findings (culture and Gram's stain) and the antibiotic sensitivity of the organisms isolated.

3.1.4. Examination of the excised material

The excised specimen was placed in a liquid medium containing thioglycollate medium (Difco 0256-01) casitone, extract of yeast, dextrose, NaCl, L-cystine, Na-thioglycollate, agar, resazurine and subsequently incubated during 10 days. If the medium exhibited turbidity some of the fluid was inoculated on a solid medium (agar plate). After inoculation, plates were incubated at 37°C and daily inspected. When different colonies developed they were subcultured to confirm the identity of the colonies.
Examination of the pathologist consisted of a description of the macroscopic appearance of the material followed by microscopic examination. The microscopic preparations were stained by Gram's technique for identification of bacteria. Micro-organisms were called Gram-positive when they resisted decolorization by alcohol. The latter had to be demonstrated by a counterstain. Lesions attached on a valve were microscopically called vegetations when they consisted of an amorphous mass composed of fibrin, platelets, leukocytes, red blood cell-debris, together with masses of bacteria. Indications for activity of infection were infiltration of a valve by mononuclear cells or larger multinuclear cells.

3.2. RESULTS

3.2.1. General information:

From August, 1972, to August, 1981, 46 patients underwent cardiac surgery in the St. Radboud Hospital during or after infective endocarditis (IE). The group consisted of 16 women and

30 men with a mean age of 36.9 years and a range of 19-67 years. The aortic valve was involved in 26 patients: 24 men and 2 women (male:female ratio 12:1). This "aortic group" (figure 8) consisted of 24 patients with pure aortic regurgitation (including 2 prosthetic valves), 1 patient with aortic regurgitation + aortic stenosis and 1 patient with aortic valve vegetations without evidence of valve dysfunction. The mitral valve was involved in 13 patients: 4 men, 9 women (male:female ratio 1:2.3).

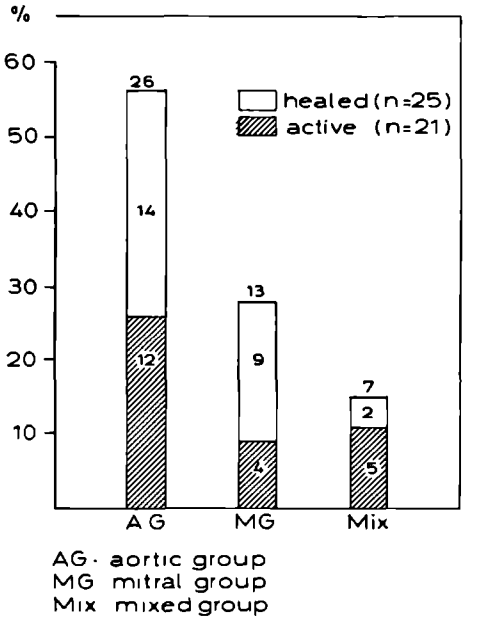


Figure 8. Valve involvement in 46 patients treated with surgery. The total number of individuals in each group is noted above - and within - the bar. Percent of the total (46) in each group is indicated on the ordinate.

This "mitral group" consisted of 11 patients with pure mitral regurgitation (including 1 prosthetic valve) and 2 patients with mitral stenosis (including 1 prosthetic valve). A "mixed group" consisted of 7 patients (2 men, 5 women): 3 patients with aortic and mitral valve involvement, 1 patient with mitral

regurgitation and tricuspid regurgitation and 3 patients with right-sided endocarditis (2 with subpulmonic stenosis, 1 with isolated tricuspid regurgitation). In 21 patients operation was performed during antibiotic treatment; these patients will be referred to as the "active group". Twenty-five patients underwent operation after completion of a course of antibiotic therapy; these patients will be referred to as the "healed group".
The 46 patients had 58 episodes of IE; 6 patients suffered twice from IE, 3 patients 3 times. Only data from the last IE will be discussed from here on. All clinical data are summarized in table 21 and table 22.

3.2.2. Symptoms and signs during last infective endocarditis (Table 2)

The duration of symptoms before admission varied from one day to 5 months. All patients had or had had fever. Often repeated short courses of antibiotic medication were given by the general physician, resulting in episodes of remission and relapse of fever. Forty-seven percent of patients had symptoms of fever, fatigue, and malaise before admission. These symptoms were often regarded (by patient and physician) as "influenza". Though there is some overlap (enhanced by the use of antibiotic therapy) in the course of events a distinction could be made whether the course of the disease was acute, semi-acute or chronic, based on symptoms and emergency of reference to a specialist. Thirteen patients suffered an acute disease with shaking chills (sometimes in combination with headache, dyspnea, nausea, vomiting and/or cough, see table 2).
Within one week these patients were admitted to hospital (in fact, 4 patients suffered chills shortly after vaginal delivery, in hospital). The disease had a semi-acute course (1-4 weeks) in 18 patients and a chronic protracted course (> 4 weeks) in 14 patients. The patients with the semi-acute or chronic form of the disease were ultimately referred to a specialist due to a long duration of unexplained symptoms, exacerbation of symptoms or the occurrence of chills or complications. Apart from,

TABLE 2. Symptoms before admission (45 pts.)

Symptoms	Duration before admission			Patients	
	≤1wk (13 pts)	1-4wk (18 pts)	>4wk (14 pts)	Total no.	% (of 45)
"Influenza" *		9	12	21	47
Shaking chills	13	4	1	18	39
Arthralgia and/or myalgia		4	3	7	16
Cough	2	1	4	7	16
Headache	2	4		6	13
Dyspnea	3	1		4	9
Nausea/vomiting	3		1	4	9
Nightsweat		1	1	2	4
Janeway lesions		1	1	2	4
Abdominal pain		1	1	2	4
Painful extremity		1	1	2	4
Visual disturbance		1	1	2	4
Hematuria			2	2	4
Loss of memory, hemiparesis		1		1	2

* Fever, fatigue, malaise.

or in combination with, the above mentioned symptoms, the following complaints were noted: headache (6 patients), arthralgia and/or myalgia (7 patients), cough (7 patients), dyspnea (4 patients), nausea with vomiting (4 patients), nightsweat (2 patients), Janeway lesions (2 patients), abdominal pain (2 patients), painful extremity (2 patients), visual disturbances (2 patients), haematuria (2 patients), hemiparesis (1 patient). The majority of the patients were referred to an internist, 7 patients were

initially seen by another specialist: twice a patient was referred to a dermatologist because of reddish (painless) spots on lower extremities (Janeway lesions); one patient was referred to the urologist because of acute pain in left hypochondrium; one patient was seen by the neurologist because of hemiparesis and symptoms of confusion, desorientation and loss of memory; another patient with persistent cough was referred to a pulmonologist; two patients visited the ophtalmologist (one because of a sudden blurring of vision of the left eye based on acute iridocyclitis with lens rupture; the other patient because of diplopia resulting from paralysis of musculus rectus internus of the left eye).

3.2.3. Physical examination during infective endocarditis (Table 3) Eighty-five percent of the patients had fever (> 38°C) on admission, but all patients developed fever (to a maximum of 40.3°C) during hospitalization. In 41 patients (89%) a cardiac murmur was heard on admission. In 24 of the 26 patients of the "aortic group" a murmur was heard on admission: the murmur was systolic at the heartbase in 4 (in only 1 patient was this murmur actually caused by aortic stenosis: at heart catheterization 22 years before IE, a gradient over the aortic valve of 35 mmHg was found); diastolic at the left parasternal border in 13; and combined systolic and diastolic in 7 patients. In 11 of the 13 patients of the "mitral group" a murmur was heard on admission: eight patients had an apical pansystolic murmur; two, a diastolic murmur; one a combined systolic and diastolic murmur. In 6 of the 7 patients of the "mixed group", murmurs were heard on admission. The murmurs of the following combinations of valve lesions were heard: aortic regurgitation and mitral stenosis in one patient; aortic- and tricuspid regurgitation with aortic- and mitral stenosis in the second; mitral and tricuspid regurgitation in the third patient. In the 2 patients with the right-sided endocarditis and subpulmonic stenosis, a systolic murmur was heard at the left second and third intercostal space. In one patient an ejection murmur was heard at the heart base. The loudness of all murmurs ranged

TABLE 3. Physical findings on admission (46 pts.)

		Patients	
		No.	%
Fever		39	85
Cardiac murmurs		41	89
Splenomegaly		8	17
Skin lesions		8	17
dermal petechiae	3		
subungual hemorrhages	3		
Janeway lesions	2		
Ophtalmologic findings (in 24 pts.)		4	17
retinal hemorrhages	2		
iridocyclitis with lens-rupture	1		
paralysis of m. rectus internus of left eye	1		
Clubbing of fingers		4	9
Systemic embolism		3	6.5
Mycotic aneurysm		2	4

from grade 1 to grade 4/6.

Skin lesions were seen in 8 patients: abdominal and/or conjunctival petechiae in 3; subungual splinter hemorrhages in 3; Janeway lesions on the lower extremities in 2 patients. No Osler nodes were seen. Enlargement of the spleen was noted in 8 patients, clubbing of fingers in 4. Twenty-four of the 46 patients were seen by an ophthalmologist, only 2 times were abnormalities seen in fundo: in 1 patient an old hemorrhage in the right upper quadrant of the right eye; in another patient some petechiae on the temporal side of the right eye-ground. No Roth spots were seen. In two other patients the ophtalmologist diagnosed iridocyclitis with lens rupture, respectively

paralysis of m. rectus internus; in both patients the left eye was involved. In 5 patients presenting symptoms (see also table 2) and signs were: painful left arm (mycotic aneurysm of arteria brachialis) in one patient; painful right leg (mycotic aneurysm at the bifurcation of arteria tibialis posterior and arteria fibularis, figure 9) in another; right hemiparesis, confusion and memory loss due to cerebral embolism in still another; acute abdominal pain based on embolism in the arteria lienalis respectively arteria mesenterica in two patients (the mycotic aneurysms and occluded middle cerebral artery and inferior mesenteric artery were demonstrated by angiography, a splenic infarction was documented by means of scintigraphy).

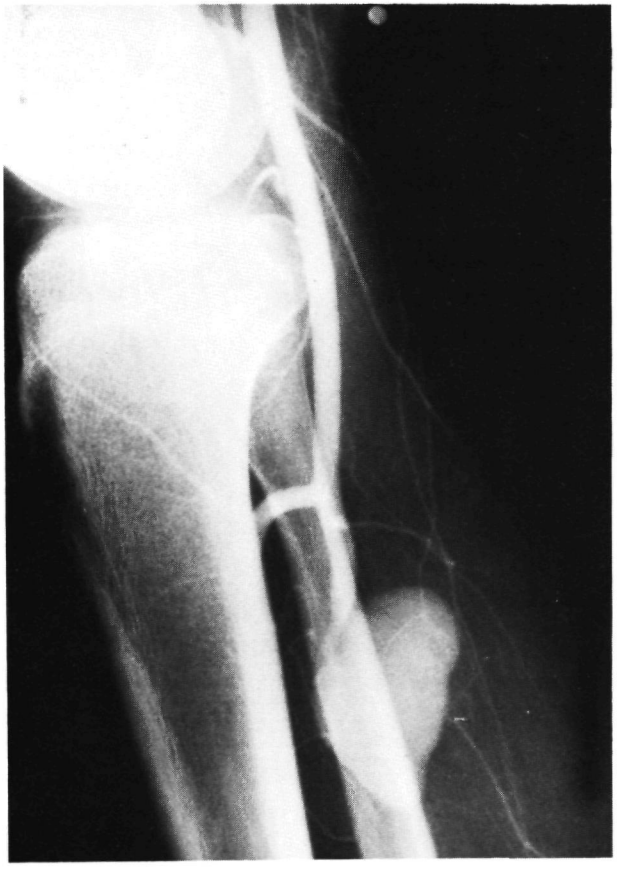


Figure 9. Right femoral arteriogram of case 6, demonstrating a mycotic aneurysm (diameter 3 to 5 cm), arising at bifurcation of posterior tibial artery and fibular artery.

3.2.4. Laboratory findings (Table 4)

Not all laboratory tests could be found in the patient records. All of the well-documented patients had an elevated ESR (> 15 mm after 1 hour). Anemia (Hb < 7.5 mmol/l) occurred in little more than one half of the patients and was normochromic and normocytic. Leukocytosis (leukocytes > 10 x 10^9/l) was found in 68%; a very high white blood cell count was seen in a patient with acute bacterial endocarditis caused by streptococcus viridans: 28 x 10^9/l. In all 41 patients (including those with normal white blood cell count) there was a shift to the left in the differential count. A rise in gammaglobulin (> 16 g/l) occurred in 37%, in alpha$_2$-globulin (> 8 g/l), in 22%. Of the 10 patients with elevated serum kreatinin (> 100 µmol/l), 6 patients had microscopic hematuria with red blood cell casts and proteinuria (indicating acute proliferative glomerulonephritis). Two of them had to be put on dialysis because of

TABLE 4. Laboratory findings on, or shortly after, admission

	Patients		
	Total*	No.	% **
Elevated sedimentation rate	41	41	100
Anemia	41	22	54
Leukocytosis	41	28	68
Hypergammaglobulinemia	27	10	37
Hyperalpha$_2$globulinemia	27	6	22
Elevated serum kreatinin	40	10	25
Rheumatoid factor	13	2	15
Immune complexes	3	3	100
Hematuria	39	12	31
Proteinuria	39	6	15

* Number of well-documented patients

** Percentages based on the total number of well-documented patients.

severe impairment of renal function (serum kreatinin 552 µmol/l respectively 1060 µmol/l). In 3 of the 10 patients with elevated serum kreatinine, an immunecomplex-test was done: circulating immunecomplexes were detected in their serum in combination with low concentration of complements C3 and C4. A Rose/Latex fixation test was performed in 13 patients; in 2 of them the rheumatoid factor was demonstrated in the serum. Both patients had a streptococcus viridans endocarditis with symptoms of fever within one, respectively two, months before admission. Hematuria with normal renal function and without proteinuria was seen in 6 patients: in 4 it was microscopic, in 2 macroscopic.

Blood cultures (Table 5)

Micro-organisms responsible for infection are tabulated in table 5. Various species of streptococci, especially those of the viridans group, predominated, followed by the staphylococci. Diphteroid was cultured in a patient with a Björk-Shiley aortic valve prosthesis; infection occurred 2 years after implantation. Only one case of fungus endocarditis caused by candida albicans and one case of gram-negative endocarditis occurred in this series. The first patient had antibiotic therapy for beta-hemolytic streptococcus endocarditis. After 3 weeks there was fever relapse and positive blood cultures for candida. In the second patient E.coli was isolated from the blood after induced abortion. Despite the negative blood cultures in six patients they were included in this study because:

a. all patients had cardiac deterioration after a febrile period, necessitating cardiac surgery,
b. the patients had pathologic findings characteristic for IE. One patient had destructed aortic valve leaflets and a small abscess cavity in the interventricular septum. In one of two patients with a bicuspid aortic valve a perforation of a cusp was seen, the other cusp contained a large vegetation; the other patient had some small vegetations on the ventricular aspect of the cusp, the other cusp being nearly completely destroyed. Two patients had ruptured chordae

TABLE 5. Microbiologic etiology (46 patients)

Causative organism		Patients No.	% 1)	% 2)
Streptococcus		28	61	70
viridans	25			
β-hemolytic group B	1			
faecalis	2			
Staphylococcus		9	19.5	22.5
aureus	6			
albus	3			
Miscellaneous		3	6.5	7.5
diphteroid	1			
candida albicans	1			
escherichia coli	1			
Unknown		6	13	

% 1) = percentage of the total patientgroup (46)

% 2) = percentage of the patients with pos. bloodcultures (40)

tendineae; in one patient some of the chordae tendineae were swollen, erythematous and adherent to each other and on the edge of the anterior mitral leaflet some smaller vegetations were found; in the other patient small vegetations were seen on the edges of both mitral valve leaflets. Microscopic examination of the vegetations in this patient revealed gram-positive cocci with signs of active inflammation (polymorphonuclear leukocytes). The vegetative lesions of the other three patients described above were histologically regarded as being healed, due to the presence of fibrin, platelets, blood cell debris and/or granulation tissue; micro-organisms were not detected in these lesions. In the sixth patient a round perforation, 1.5 cm in diameter, was found in the anterior mitral leaflet.

c. all six patients had antimicrobial therapy (prescribed by the general physician) within 2 weeks before admission and it is a known fact that administration of antimicrobials in the 2-week period prior to blood culture reduces the incidence of positive blood culture (see chapter 2, 3.2.1.).

3.2.5. Pre-existent cardiac lesions (Table 6)
Underlying organic heart disease was found in 27 of the 46 cases (59%). Earlier inserted prosthetic material was present in five of the 46 cases (11%). No pre-existent abnormalities were found in 14 of the 46 cases (30%).

Congenital heart disease was the most common cardiac disorder (14 of 46 cases): 11 with a congenital bicuspid aortic valve (all men), one with atrial septal defect of the secundum type, and two with subpulmonic stenosis.

TABLE 6. Preexistent cardiac lesions (46 patients)

	Patients	
	No.	%
Congenital	14	30
bicuspid AV	11	
IPS	2	
ASD II (+ MV prolapse)	1	
Rheumatic	10	22
Prosthetic material	5	11
prosthetic valves	4	
Carpentier ring	1	
Miscellaneous	3	7
dissecting aneurysm	1	
MV prolapse	1	
myxoma aMV	1	
No previous lesion demonstrable	14	30

Rheumatic valvular disease was the next commonly identified underlying lesion (ten of 46 cases). Valvular deformities were interpreted as rheumatic in origin in ten patients. Five patients suffered from rheumatic attack(s) in the past, resulting twice in bicuspid aortic valves, one time in bicuspid aortic valve in combination with mitral stenosis; in one patient the trileaflet aortic valves were thickened and shortened; in the fifth patient the mitral leaflets were thickened, especially along the line of closure, with stretched chordae tendineae. In five patients without a history of rheumatic fever the following deformities were encountered at operation: in three patients the mitral valve leaflets were fused at the commissures (two with mitral stenosis, and one with thickened calcified anterior mitral leaflet with slight fusion of the posterior commissure); in one patient the valve leaflets were thickened and the chordae tendineae shortened and retracted; in the fifth patient calcification at the commissural side of the anterior mitral leaflet was found in combination with severe scarring and shortening of the posterior mitral leaflet.

In five patients prosthetic material was inserted in the heart before the occurrence of endocarditis. The type of prosthetic material utilized and the location of insertion were: Björk-Shiley aortic valve prosthesis in two patients; Björk-Shiley mitral valve prosthesis in one patient; Starr-Edwards mitral valve prosthesis in another patient; Carpentier ring in mitral position in still another patient. Two patients developed "early" (< 2 months after operation) endocarditis: respectively 2½ weeks after implantation of a Carpentier ring and 2 weeks after insertion of a mitral valve prosthesis. In 3 patients a "late" (> 2 months after operation) endocarditis occurred: respectively 2, 8, and 9 years after implantation of prosthetic valves.

In two patients the underlying lesion was mitral valve prolapse: one had a large voluminous anterior mitral leaflet which could be pulled into the left atrium by the surgeon; the second patient was known to have an atrial septal defect and a mid- to late-systolic click and murmur one year before IE was contracted.

In one patient a pedunculated tumor attached on the anterior mitraa leaflet was detected at operation, and this appeared to be a myxoma according to microscopic examination. In another patient the proximal aorta was dilated with a dissection of the wall immediately above the aortic valves, located at the outer large curve of the aortic wall and limited to the first half of the ascending aorta. The concomitant dilatation of the aortic annulus produced valvular regurgitation. I assume here that the dissection was the underlying (predisposing) lesion for IE.
In 30% of the cases no pre-existent abnormality could be seen on cardiac valves: this was the case in nine patients in the aortic group, in two patients in the mitral group, and in three patients in the mixed group. In general, valvular damage was extensive in these cases, making it impossible to say with certainty that no previous abnormalities were present.

3.2.6. Portals of entry (Table 7)
A portal of entry was determined in 18 of the 46 cases (39%).
A portal of entry was suspected in 15 of the 46 cases (33%).
No portal of entry for micro-organisms could be determined in 13 of the 46 cases (28%).
Periodontitis and dental caries as found at physical examination in 15 patients could have been a possible portal of entry.
The portals of entry that have been identified, 18 cases, show a certain variety. Dental treatment caused a portal of entry in six cases. Five patients had had a dental extraction and in one the teeth had been cleaned by the dentist. Other causes were vaginal delivery (four cases), induced abortion (one case), catheterization of the bladder (one case), (extra)cardiac operation (five cases) and a skin abscess (one case). In all these 18 cases symptoms of IE followed within 3 weeks after the infection with micro-organisms. In the two patients, who underwent cardiac surgery, cephalotin was given during the peri-operative period as described re 3.1.3. As far as I could find the other patients had not had an antibiotic prophylaxis. For the most part, it was not known that they had an under-

TABLE 7. Portal of entry (46 patients)

		Patients	
		No.	%
Oral cavity		(21)	(46)
dental work	6		13
(dental caries)	(10)		
(periodontitis)	(5)		
Genitourinary tract		6	13
delivery	4		
induced abortion	1		
catheterization of the bladder	1		
Extra cardiac operation		3	7
inguinal hernia	1		
sinus pilonidalis	1		
vasectomy	1		
Cardiac operation		2	4
Skin abscess in heroin addict		1	2
Unknown		13	28

lying heart disease. A few remarks are added about the two patients that had been given an antibiotic prophylaxis. A patient that had a Carpentier mitral ring implanted got fever 2½ weeks after the operation. Blood cultures were positive (streptococcus viridans). No special portal of entry could be found. A patient that had a mitral valve prosthesis implanted, got fever 2 weeks after operation. Blood cultures were positive (staphylococcus aureus). The source was a wound infection at the site of the (removed) left atrial line, which resulted in early prosthetic valve endocarditis.

3.2.7. Antibiotic treatment (Table 8)

Twenty-one patients classified as having "active" endocarditis underwent operation during antibiotic therapy. The duration of pre-operative antimicrobial therapy varied from 1 week to 7 weeks (average: 4 weeks). Twenty-five patients classified as having "healed" endocarditis underwent operation after intervals varying from 2 weeks to 16 years after completion of antibiotic therapy (average: 2.4 years). The patients in this last category received a complete course of antibiotic treatment during the period of their infective endocarditis (4-6 weeks). There was one exception: a patient with high fever and sterile blood cultures, thought to have pneumonia, received ampicillin for only one week. All antibiotics were given parenteral. Streptococcus infection was treated by penicillin alone in 15 patients; 12 patients were treated with penicillin in combination with streptomycin or gentamycin or kanamycin. Because of persisting temperature or allergy, a second choice of antibiotic treatment consisted of cephalofin, oxacillin or vancomycin. Staphylococcus infection was treated with penicillinase-resistant pencillin alone (oxacillin) or in combination with other antimicrobial agents; either by penicillin and gentamycin, or by cephalosporin with other antibiotics (table 8). The patient with prosthetic valve endocarditis caused by diphteroid-species was treated with penicillin, oxacillin, and gentamycin. For the E.coli endocarditis three different combinations of antibiotic drugs were used (table 8). The patient with candida albicans infection was treated with 5-fluorocytosine in combination with amphotericin B. Patients with sterile blood cultures were treated with combinations of different antibiotic agents (see table 8). After institution of antibiotic treatment, the temperature was normal within 1 week in 26 of the 46 patients; in eight patients the normalization took 10 days to 1 month, while in 12 patients of the "active group", the temperature was higher than 37.5^{o}C until operation, despite antibiotic treatment.

TABLE 8. Antibiotic treatment (46 patients)

Organism	Antibiotic drug 1st choice	2nd choice	3rd choice	Patients No.	Act.	Hea.	Total duration AB-treatment till oper. (Act.)	Time elapse between last AB-dose and oper. (Hea.)
str.viridans*				26				
	PCN				1		4 wk	
	"	Ox+GM			1		5 wk	
	"+SM or GM				4		1wk,2wk,6wk(2x)	
	"					14		2wk-16 years
	"+SM or KM	CP+GM				6		
str.faecalis				2				
	"+SM	VC			1		3wk	
	"+"					1		2.5 years
st.aureus				6				
	Ox	CP+AMK			1		7wk	
	CP+GM	Ox+LN+RF			1		6wk	
	Ox+KN				1		2.5wk	
	Ox+CL+RF	VC	CP+GM		1		3wk	
	Ox	CP+GM				1		4.5 months
	CP+Amp	Ox+CP+GM				1		6 months
st.albus				3				
	Ox+GM				2		2wk,3wk	
	PCN+GM				1		1.5wk	
Diphteroid	PCN+Ox+GM			1	1		5wk	
Candida	AmB+5-FC			1	1		7wk	
E.coli	CP+GM+CL	CL+AMK	Amp+CP+AMK	1	1		6wk	
Unknown				6				
	PCN+GM				1		1wk	
	Amox	Amox+GM	PCN+SM		1		5wk	
	" +SM	" +Myc	" +GM		1		5.5wk	
	"	PCN+SM			1		4.5wk	
	Amp					1		2.5 months
	PCN					1		4.5 years
							1wk-7wk (mean 4wk)	2wk-16years (mean 2.4years)

* including the patient with β-hemolytic streptococ.

AmB = Amphotericin B
AMK = Amikacin
Amox = Amoxycillin
AMP = Ampicillin
CL = Clindamycin
CP = Cephalotin
5-FC = 5-Fluorocytosin
GM = Gentamycin
KN = Kanamycin
LN = Lincomycin
Myc = Myconasol
Ox = Oxacillin
PCN = Penicillin
RF = Rifampin
SM = Streptomycin
VC = Vancomycin

3.2.8. Change in the cardiac situation during or since last episode of infective endocarditis (Table 9)

From the 46 patients there were 33 with a "change" in the cardiac situation. In 19 patients this change occurred during antibiotic therapy. The interval between date of admission and manifestation of the change was 3 days to 6 weeks (average, 2.6 weeks). In 14 patients the change occurred 1 week to ± 13 years (average, 2 years) after completion of antibiotic therapy. The "change" consisted of: a) a changing murmur in 23 patients (eight with a new murmur; 15 with a louder murmur); and b) an increase in heart-lung ratio (as indicated by chest X-ray, of > 5% compared with the chest X-ray made on admission), in 29 patients. Despite a definite change in cardiac situation (louder murmur, increased HLR, severe heart failure) 3 months after a (misjudged) IE, I did not include case 11, since his fever during his second admission was considered to be based on a second (culture negative) IE. So strictly speaking, the "change" did not take place during the last IE.

TABLE 9. Change in cardiac situation in 33 out of 46 patients

	During AB* (N=19)	After AB** (N=14)	Total (N=33)	% (of 33)
Changing murmur	17	6	23	70
Increase in HLR	16	13	29	88
Heart failure	18	14	32	97
mild	2	6	8	
moderate	10	5	15	
severe	6	3	9	

* During antibiotic therapy

** After completion of antibiotic therapy

Thirty-two patients developed some degree of heart failure: Mild heart failure occurred in eight patients; moderate in 15; and severe, in nine (for definition of the degree of heart failure see chapter 3, re 1.1). In 16 of the 24 patients with moderate to severe heart failure, the severity increased gradually in time; eight patients (seven with aortic regurgitation, one with mitral regurgitation) experienced an abrupt increase in the degree of heart failure (an attack of cardiac asthma) after a period of apparently stable normal cardiac function or mild heart failure. In five patients this sudden deterioration occurred 3 days to 5 weeks after admission and during antibiotic therapy, in three patients respectively 2.5 weeks, 5 weeks and 1 year after completion of antibiotic therapy.

3.2.9. Pre-operative evaluation

3.2.9.1. Physical examination (Table 10)

All patients with severe aortic and/or mitral valve involvement were dyspnoic at rest.

The diastolic murmur heard at the left parasternal region as a result of aortic regurgitation was, in general, loud (grade 3/6 or 4/6). In one patient with severe aortic regurgitation and impaired cardiac function, there was only a grade 1/6 diastolic murmur. In all patients with aortic regurgitation and severe heart failure, the Duroziez sign and capillary pulse were found to be positive. In nearly all (eight of nine) patients with moderate heart failure, and in five of eight patients with mild heart failure, these signs were positive. Of the 24 patients with pure aortic regurgitation, 19 patients had a pulse pressure of more than half the systolic pressure. Eleven of the 26 patients with severe and moderate heart failure had a sinus tachycardia.

Loud apical systolic murmurs due to mitral regurgitation (grade 3-4/6) were heard in ten of the 12 patients in the mitral group (83%) with severe, moderate and even mild heart failure. An apical diastolic murmur was heard in one patient with mitral stenosis and in one patient with a Starr-Edwards mitral valve prosthesis.

TABLE 10. Physical examination and degree of left-sided heart failure just before operation (43 pts.)

Objective findings		Degree of LHF									
		Severe (N=11)			Moderate (N=15)			Mild (N=13)		Absent (N=4)	
		AG (N=6)	MG (N=2)	Mix (N=3)	AG (N=9)	MG (N=5)	Mix (N=1)	AG (N=8)	MG (N=5)	AG (N=3)	MG (N=1)
murmurs of:	grade										
AR	1	1									
	2			1^{O}				3^{+}		2 (PV)	
	3	2		1	9		1^{*}	5			
	4	3									
AS	2			1^{O}				1^{+}			
EM	2									1	
MR	2			1^{*}		$1 (PV_I)$					
	3		1	1^{Δ}		2			3		
	4		1			1			2		
MS	1										1
	2			1^{O}		$1 (PV_{II})$	$1^{\circledast}$				
Duroziez sign		6		1	8			5			
Capillary pulse		6		1	8			5			
Pulse pressure >½ systolic pressure		6			8			5			
Heartrate >100		5	1		4	1					

EM = Ejection murmur: systolic murmur at the heart base, not proven to be based on aortic stenosis.

\+ case 26: AR + AS (PV_I) case 39: PV regurgitation

* case 42: AR + MR (PV_{II}) case 32: PV stenosis

$^{\circledast}$ case 44: AR + MS

O case 45: AR/AS + MS

Δ case 41: MR + TR

The murmurs of the following combinations of valve lesions were heard in the mixed group: tricuspid regurgitation; tricuspid- and mitral regurgitation; aortic- and mitral regurgitation; aortic- and tricuspid regurgitation plus aortic- and mitral stenosis; aortic regurgitation and mitral stenosis, sub-pulmonic stenosis.

3.2.9.2. Echocardiographic parameters and degree of heart failure (Table 11)

Thirty-five out of 43 patients with involvement of the left heart underwent pre-operative echocardiography. When only those patients with volume overload of the left ventricle due to valve insufficiency are selected, 29 patients remain (table 11): all six patients with severe heart failure and pure aortic regurgi-

TABLE 11. Echoparameters and degree of heart failure in 29 patients with volume overload of the left ventricle

	Degree of LHF								
	Severe (N=9)			Moderate (N=9)		Mild (N=9)		Absent (N=2)	
Echocardio-graphy	AG (N=6)	MG (N=2)	Mix (N=1)	AG (N=7)	MG (N=2)	AG (N=6)	MG (N=3)	AG (N=2)	
ECMV	6			3					
LVEDD									
50-59 mm	1	1					1	2	
60-69	1	1	1*	2	2	1	2		
70-79	3			2		5			
⩾ 80	1			3					
FS %									
0.20-0.29	2			1					
0.30-0.39	1	1	1*	2	2	3		2	
0.40-0.45	1			2		3	3		
0.46-0.55	2	1		2					
Ratio LA/Ao									
1-1.2	5			4		6		2	
1.3-1.5		1	1*	3			3		
1.6-2	1	1			2				

* case 42, see table 10

tation exhibited an early closure of the mitral valve; three of the six patients in the aortic group with moderate signs of heart failure showed early closure of the mitral valve. A normal mitral valve closure was seen in those with mild and absent heart failure. Looking at the left ventricular end-diastolic dimension in the patients with pure aortic regurgitation (21 patients), mitral regurgitation (seven patients) or combined aortic and mitral regurgitation (one patient), 24 of these 29 patients had a dimension of 60 to 85 mm. This dimension was normal (< 55 mm) in two patients with severe heart failure; on the other hand, this dimension was largely increased (> 70 mm) in five patients with aortic regurgitation and only mild heart failure; in one patient with moderate heart failure the left ventricular end-diastolic dimension was 95 mm. The fractional shortening of the left ventricle was very low (< 0.30%) in three patients with aortic regurgitation: 0.20% and 0.25% in two with severe heart failure, 0.22 in one with moderate heart failure. Five patients had a high fractional shortening (> 0.45%) with a marked hyperkinetic left ventricle.

The left atrium/aorta ratio was increased in only 19% of the patients with aortic regurgitation (four out of 21). All patients with some degree of mitral regurgitation showed an enlarged left atrium and subsequently an increased LA/Ao ratio. This difference in LA/Ao ratio between aortic group and mitral group might be explained as follows: both aortic group and mitral group were composed of patients with varying degree and duration of valve regurgitation. In case of chronic, or gradually increasing, aortic regurgitation the adaptive response of the left ventricle to handle large diastolic volumes and stroke volumes, often results in little increase in end-diastolic pressure. Left atrial pressures therefore, are generally not high and left atrial enlargement will not take place. In case of acute aortic regurgitation premature closure of the mitral valve protects the left atrium from backward transmission of the greatly elevated LV end-diastolic pressure. On the other hand, in case of mitral regurgitation the regurgitant blood volume is directly transmitted to the left atrium. The volume

overload of the left atrium results in its dilatation. Hence in mitral regurgitation the degree of enlargement of the left atrium depends on the duration and degree of regurgitation and on the compliance of its wall. Enlargement will occur earlier in the course of valve regurgitation as compared with aortic regurgitation.

3.2.9.3. Cardiac catheterization (Table 12)

Cardiac index, pulmonary artery pressure and mean pulmonary capillary wedge pressure were measured in 35 patients. The cardiac index was rather low in the patients with severe heart failure; the mean value was definitely better in the moderate and mild heart failure group, and was normal in the patients without heart failure (see table 12). The systolic pulmonary artery pressure and the mean pulmonary capillary wedge pressure were high in the severe heart failure group (respectively 73, 31.5 mmHg) compared to the moderate and mild heart failure group (respectively 40.5, 19 and 34, 15.5 mmHg). Also the mean value of the aortic systolic pressure was the lowest in the severe heart failure group (101 mmHg); higher pressures were measured in the moderate and mild heart failure group. Thus, as was to be expected, a decrease in the degree of heart failure parallelled an improvement in hemodynamic parameters.
Supravalvular aortography was done in 18 patients: in 12 the aortic regurgitation was grade 3+; in five, grade 4+; in one, grade 2+.
The following abnormalities were seen with aortography: in two patients, accumulation of contrast in the left ventricle myocardium just below the aortic valves with a diameter of $\pm$ 1 cm (figure 10); in one patient, a fistula from aorta to right atrium in combination with an aneurysm of sinus Valsalva of the non-coronary cusp (figure 11); in another patient, a diastolic prolapse of one of the aortic cusps into the left ventricular outflow tract; in still another patient a large "bulge" at the level of the right coronary cusp, initially thought to represent an aneurysm of the right coronary sinus of Valsalva (figure 12).

TABLE 12. Cardiac catheterization and degree of left-sided heart failure in 37 out of 43 patients with involvement of the left heart

Cardiac catheterization	Degree of LHF: Severe AG	Severe MG	Severe Mix	Moderate AG	Moderate MG	Mild AG	Mild MG	Absent AG	Absent MG
Ao Angiography (N=18)									
AR grade 2+								1	
3+			$2^{o,*}$	3		7			
4+	2			3					
LV Angiography (N=21)									
MR grade 0	1		1^{o}	3	1 (PV)	5			1
2+			1*						
3+					2		5		
4+		1							
CI (N=35)	(N=5)	(N=2)	(N=2)	(N=8)	(N=4)	(N=8)	(N=4)	(N=1)	(N=1)
		1.5			2.4		2.5		2.8
mean value	1.7	1.1	1.8	2.4	2.5	2.6	2.4	3	2.7
PCWP (N=35)	(N=5)	(N=2)	(N=2)	(N=8)	(N=4)	(N=8)	(N=4)	(N=1)	(N=1)
		31.5			19		15.5		11.5
mean value	32	25	37.5	21	17	12	19	10	13
SPAP (N=35)	(N=5)	(N=2)	(N=2)	(N=8)	(N=4)	(N=8)	(N=4)	(N=1)	(N=1)
		73			40.5		34		29
mean value	65	67	87.5	45.5	35.5	24	44	28	30
SAP (N=28)	(N=3)	(N=1)	(N=2)	(N=6)	(N=3)	(N=7)	(N=4)	(N=1)	(N=1)
		101			120		130		140
mean value	99	105	100	126	114	120	140	180	100

0 case 45
* case 42
(PV) case 32
} see table 10

PCWP = pulmonary capillary wedge pressure
SPAP = systolic pulmonary artery pressure
SAP = systolic aortic pressure

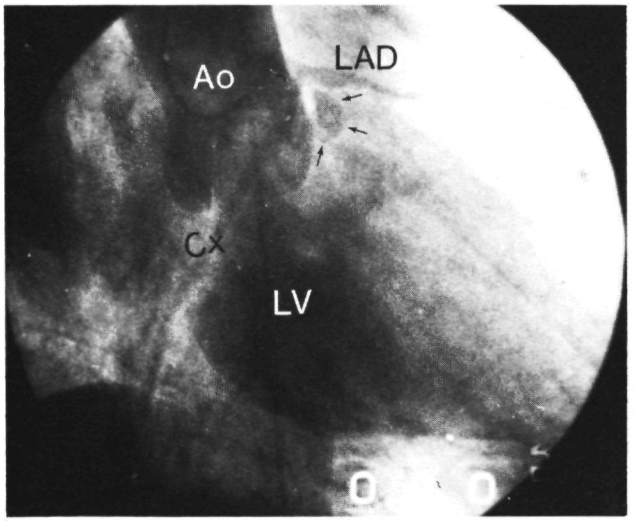
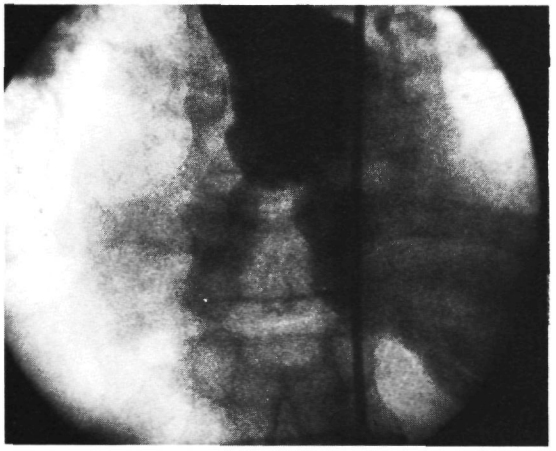


Figure 10. Aortogram from case 42 (right anterior oblique view). Following injection of contrast material into the ascending aorta (Ao), the left coronary artery system is visualized; there is a dense opacification of the left ventricle (indicating grade 3+ aortic regurgitation) and contrast material is deposited in a small cavity (arrows), located in the proximal part of the ventricular septum. LAD = left anterior descending coronary artery; Cx = circumflex artery ; LV= left ventricle.

Left ventricular angiography was done in 21 patients: in eight with mitral regurgitation, in one with a slight mitral stenosis, in one with a prosthetic mitral valve-stenosis; in 11 with aortic valve pathology. In this last patient group the aortic valve was passed by the catheter to enter the left ventricle making a left ventricle angiogram possible. In nine "healed" patients this occurred 2.5 months to 16 years (average 3 years) after completion of antibiotic treatment. In two "active" patients (one pure aortic regurgitation, one aortic regurgitation and stenosis) the aortic valve was passed during antibiotic treatment. In these 11 patients no embolic complications occurred. In only one of these 11 patients was mitral regurgitation grade 2+ detected. Seven patients with mitral regurgitation and mild



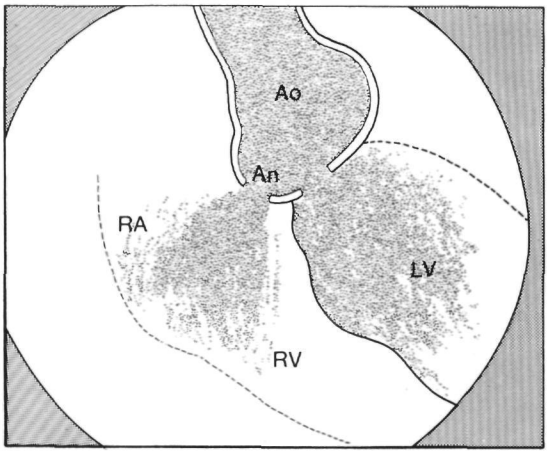
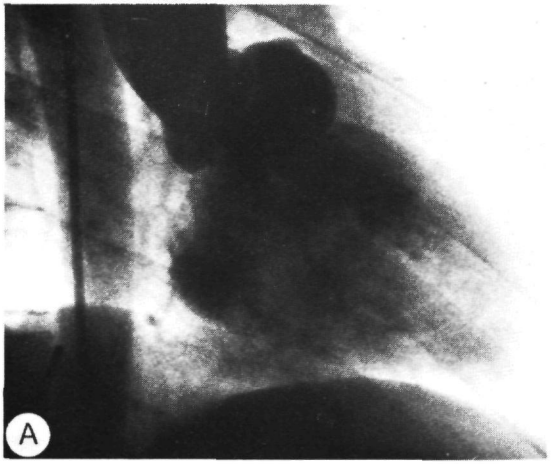
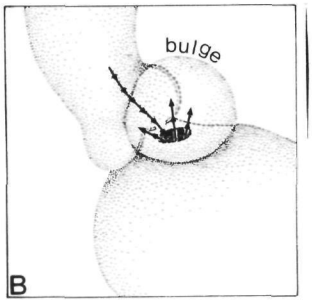


Figure 11. Aortogram and schematic drawing from case 12. Frontal projection during diastole, showing an aneurysm (An) of the non-coronary sinus of Valsalva with opacified bloodregurgitation into the right atrium (RA). The dashed line delineates the outer border of the right side of the heart. The left ventricle (LV) is also opacified due to aortic regurgitation.





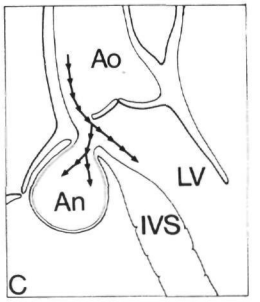


Figure 12. Aortogram and schematic, idealized, drawings from case 26 (in this patient only one aortogram, in right anterior oblique projection, was obtained). Supravalvular injection of contrast material reveals a "bulge" at the level of the right coronary sinus of Valsalva. This "bulge" was caused by a large aneurysm of the proximal part of the interventricular septum, extending into the outflow tract of the right ventricle. Opacification of the left ventricle indicates a grade 3+ aortic regurgitation. The aneurysm was filled with the regurgitant opaque material (arrows in panels B and C).

or moderate heart failure showed a regurgitation grade 3+; in the one with severe heart failure, the mitral regurgitation was grade 4+.

The following abnormalities were seen with left ventricular angiography: a prolapse of the posterior mitral leaflet to the left atrium in systole (one patient); some calcification of the posterior mitral leaflet in another patient. In the one patient with slight mitral stenosis no abnormalities could be seen on the left ventricular angiography except for some impairment in the opening of the mitral valve leaflets during diastole. Because of thick echoes seen on the anterior mitral leaflet on the M-mode echocardiogram, additional pulmonary artery angiography was done and after some delay in time, filling of the left atrium with contrast material was filmed: a cherry-sized filling defect in the opaque material was seen on the posterior commissural side of the anterior mitral leaflet. In the patient with dysfunction of the Starr-Edwards mitral valve prosthesis (model 6300) left ventricle angiography did not reveal abnormalities, the poppet motion was not impaired; however, a high diastolic gradient across the prosthesis was found (15 mmHg) with a calculated area of the valve orifice of 1.5 cm^2 (normal values for this kind of prosthetic valve in mitral position are: average gradient 5 mmHg, range 3-9; average valve area 2.6 cm^2, range 1.9-3.5; Kloster et al, 1970).

Of the 21 patients classified as having "active" endocarditis, 13 underwent catheterization of the right side, seven of the left side with angiography; in only one coronary angiography was done. Eight patients underwent surgery on the basis of echocardiographic and clinical findings without prior cardiac catheterization. The reason why left-side catheterizations and coronary angiography were performed so sparingly in this "active" patient group was not always clear to me. An important factor must have been that some patients were severely ill and catheterization was considered to be too great a risk.

Of the 25 patients classified as having "healed" endocarditis, 22 underwent catheterization of the right side, 21 of the left side with angiography and in nine, coronary angiography was

performed; hence in this last group a more extensive invasive investigation was carried out.

3.2.10. Indications for operation (Table 13)

Heart failure predominated as the most serious manifestation of IE and formed the main indication for operation in most patients of this series (87%). Left-sided heart failure occurred in 39 patients; only one patient (with isolated tricuspid regurgitation) exhibited failure of the right side of the heart. Heart failure was the only indication for operation in 30 patients; in ten patients concomitant indications were: systemic emboli (two patients, to brain and spleen) and persistent infection (seven patients). In one patient with staphylococcus aureus endocarditis, all 3 features were present: moderate heart failure, persistent infection and embolization (to a finger). Other indications were:

1) persistent infection (fever, despite antibiotic treatment and in the absence of a site of infection other than a cardiac structure). This was the only indication in a patient

TABLE 13. Indications for operation (46 patients)

		Patients	
		No.	%
Heart failure		40	87
"	alone	30	
"	+ systemic emboli	2	
"	+ persistent infection	7	
"	+ persistent infection + syst. embolus	1	
Persistent infection		5	11
"	alone	1	
"	+ PV leak	2	
"	+ pulmonary emboli	2	
Systemic embolus		1	2

with gram-negative bacteremia and a large vegetation on the aortic valve, detected by echocardiography. Concomitant indications were: changing murmur during antibiotic treatment (in two patients with aortic prosthetic valves) and pulmonary emboli (in two patients with subpulmonic stenosis and vegetations in right ventricular outflow tract and on pulmonic valve).

2) systemic embolus (to inferior mesenteric artery) in a patient with mild mitral stenosis.

3.2.11. Operative findings

3.2.11.1. Pathologic features observed at operation (Table 14, figure 13)

A. Native valves

In 46 patients, 49 valves and supporting structures were involved (28 aortic valves, 15 mitral valves, two pulmonic valves, four tricuspid valves). In the 21 patients of the active group 24 "active" valves were involved; in the 25 patients of the healed group 25 "healed" valves were involved.

On these 49 valves, 89 "abnormalities" were seen (1.8 abnormality per valve). These "valve abnormalities" consisted of (in order of frequency):

a) destruction and/or perforation
b) vegetations
c) deformity (including bicuspid aortic valve), and/or scarring, calcification
d) rupture of chordae tendineae
e) mitral valve prolapse.

Ad a)

Twenty-eight valves appeared to be destructed and/or perforated (57%): in 21 (75%) of the 28 patients with aortic valve pathology; in five (33%) of the 15 patients with mitral valve pathology; and in two of the four patients with tricuspid valve pathology. Valve destruction occurred in 12 of the 24 "active valves" (50%) and in 16 of the 25 "healed valves" (64%).

TABLE 14. Pathologic findings observed at operation (46 patients)

A. Native valves (N=49)	Aortic valve (N=28) Act. (N=13)	Hea. (N=15)	Mitral valve (N=15) Act. (N=6)	Hea. (N=9)	Pulm.valve (2) Act. (N=2)	Tric.valve (N=4) Act. (N=3)	Hea. (N=1)	Total no. of valves (49) Act. (N=24)	Hea. (N=25)
1. destruction and/or perforation	10	11	1	4		1	1	12(=50%)	16(=64%)
2. vegetations	11	6	5	2	2	1		19(=79%)	8(=32%)
3. deformity and/or scarring,calcification	4	1	2	5		1		12*(=50%)	12*(=48%)
4. chordal rupture			3	5				3(=12.5%)	5(=20%)
5. mitral valve prolapse			1	1				1(=4%)	1(=4%)
								Patients	
								No.	%
B. Prosthetic valves (N=4								4	9
1. dehiscence	2		1						
2. fibrosis				1					
C. Congenital abnormalities (N=16)									
1. bicuspid aortic valve	5	6						11	
2. ASD II								1	
3. discrete subaortic stenosis								1	14pts. 30
4. infundibular pulmonic stenosis								2	
5. small VSD								1	
D. Miscellaneous(N=14)									
1. necrotic annulus								6	
2. (old) abscess cavity								5	12pts. 26
3. sinus of Valsalva aneurysm								1	
4. vegetations in RVOT								2	

* included are the congenital bicuspid aortic valves

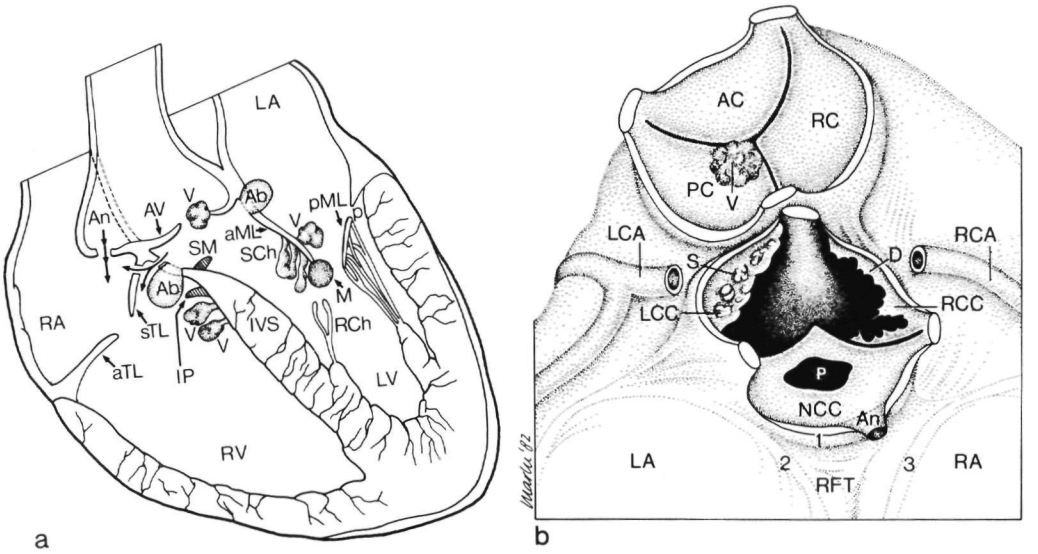


Figure 13. Schematic portrayal of abnormalities found at surgery.
a. Frontal section of the heart. b. Transverse section at the level of the aortic and pulmonic valves, viewed from above. Abbreviations of the abnormalities: Ab = abscess cavity (erosive aneurysm); An = aneurysm of sinus of Valsalva; D = destruction; IP = infundibular pulmonic stenosis; M = myxoma; P = perforation; RCh = ruptured chordae tendineae; SCh = swollen chordae tendineae; S = scarring and calcification; SM = subaortic membrane; V = vegetation. The other abbreviations are summarized in "list of abbreviations". Ciphers indicate annulus fibrosus of: aortic valve (1) mitral valve (2), tricuspid valve (3) RFT = right fibrous trigone.

Ad b)

Vegetations were found on 27 valves (55%): in 17 (61%) of the 28 patients with aortic valve pathology; in seven (47%) of the 15 patients with mitral valve pathology; in both patients with pulmonic valve pathology; and in one of the four patients with tricuspid valve pathology. They were seen 19 times on "active valves" (79%) and 8 times on "healed valves" (32%).

Ad c)

Twenty-four valves appeared to be deformed (included are bicuspid aortic valves), scarred and/or calcified (49%): in 16 (57%) of the 28 patients with aortic valve pathology (14 bicuspid

aortic valves - 11 congenital, three rheumatic -; twice, thickened tricuspid aortic leaflets); in seven (47%) of the 15 patients with mitral valve pathology (three times, mitral stenosis; one time, thickened calcified anterior mitral leaflet with slight fusion of the posterior commissure; twice, thickened anterior and posterior mitral valves; one time, calcification at the commissural side of the anterior mitral leaflet with severe scarring and shortening of the posterior mitral leaflet); and in one of the four patients with tricuspid valve pathology (thickened, retracted valves). These lesions occurred 12 times on "active valves" (50%) and 12 times on "healed valves" (48%).

Ad d)

Rupture of chordae tendineae of the mitral valve was seen in eight patients: three times, "active valves" were involved (12.5%); five times, "healed valves" (20%). In one patient a myxoma was attached to the disrupted anterior mitral leaflet.

Ad e)

Only two patients (= 4% of the valve abnormalities; = 12% of the patients with mitral valve pathology) fulfilled the criteria of "surgical prolapse". In these cases large voluminous valves without chordal rupture were seen during operation; these valves could easily be pulled into the left atrium by the surgeon. In one patient both leaflets were thickened and voluminous; chordae tendineae were stretched, but intact (figure 18). This patient had suffered an acute rheumatic attack in the past. In the other patient with a marked voluminous anterior mitral leaflet, pathologic examination revealed mucoid degeneration of both leaflets.

B. Prosthetic valves

In the four patients with prosthetic valve endocarditis, dehiscence occurred in three patients (two aortic-, one mitral valve-prosthesis); excessive fibrous ingrowth at the base of the cage of a mitral Starr-Edwards prosthesis produced a stenotic prosthesis orificium in a fourth patient.

C. Congenital abnormalities

Sixteen congenital abnormalities were found on operation in 14 patients. The bicuspid aortic valves found during operation in 11 patients were assumed to be congenital because these patients did not have a history of rheumatic fever. The next congenital malformations were seen in four patients: an atrial septal defect involving the region of the fossa ovalis (ostium secundum defect); a subaortic membrane of fibrous tissue; an anomalous mass of muscle in the outflow tract of the right ventricle, dividing it into two chambers (thus causing subpulmonic stenosis; figure 20); a tubular stenosis of the right ventricular outflow tract with hypertrophic crista supraventricularis; a small defect in the membranous portion of the interventricular septum, with left ventricular-right atrial communication via an associated defect in the septal leaflet of the tricuspid valve.

D. Miscellaneous abnormalities

In 12 patients, 14 abnormalities related to the infective process were observed. In six patients, the annulus ("valve ring") appeared to be of bad quality, i.e., partly necrotic.
The aortic annulus was involved in five patients (four with native valve endocarditis, one with prosthetic valve endocarditis); the mitral annulus in one patient (with prosthetic valve endocarditis). In five patients old abscess cavities (deep erosions) were seen with orifices just below the aortic valves in the interventricular septum (in four patients in the upper part of the septum; in one patient in the atrioventricular part of the membranous septum just near the anterior mitral leaflet). An aneurysm of the non-coronary sinus of Valsalva, was found to have ruptured into the right atrium in one patient. In two patients (with right-sided IE), vegetations were observed in the right ventricular outflow tract.

3.2.11.2. Relationship between echocardiographic findings and pathologic features (Table 15)

In 38 patients pre-operative echocardiography was performed: in four with prosthetic valve dysfunction and in 34 with native

TABLE 15. Correlation of findings at surgery and echocardiography in 38 patients

	Surgical findings	Echocardiographic findings
A. Native valves (34pts.)	39 valves	39 valves
Aortic valve	(N=25)	(N=25)
a. vegetation	16	10 (+2xe.e. in LVOT)
b. destruction	10	8 (+2xe.e. in LVOT)
perforation	11	-
c. bicuspid (deformed)	14	7 (+1xe.e. in LVOT)
Mitral valve	(N=11)	(N=11)
a. vegetation	6	2
b. perforation	2	-
destruction	1	-
c. deformed/calcified	4	4
d. chordal rupture	7	5
e. prolapse	1	1
Pulmonic valve	(N=2)	(N=2)
vegetation	2	2
Tricuspid valve	(N=1)	(N=1)
vegetation	1	1
B. Prosthetic valves(4pts.)	(N=4)	(N=4)
Aortic Bj-Sh 2x	partly dehisced	Diastolic fluttering aMV (2x)
Mitral Bj-Sh 1x	dehiscence 1/3 circumference	A2-MVO* interval shortened Hyperkinetic LV
St-Ed. 1x	fibrous tissue ingrowth + destruction clothing	Dilated left atrium
C. Congenital abnormalities(2pts.)	(N=4)	(N=2)
a. discrete subaortic stenosis	1	-
b. infundibular p.s.	2	2
c. small VSD	1	-
D. Miscellaneous (12pts.)	(N=14)	(N=4)
a. necrotic annulus	6	-
b. abscess cavity	5	1
c. rupt. sinus of Valsalva	1	1
d. vegetations in RVOT	2	2

* A2-MVO = interval between aortic valve closure and mitral disc opening.

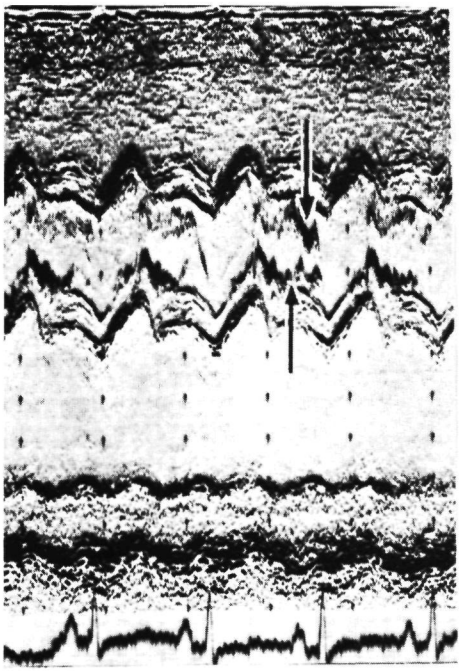
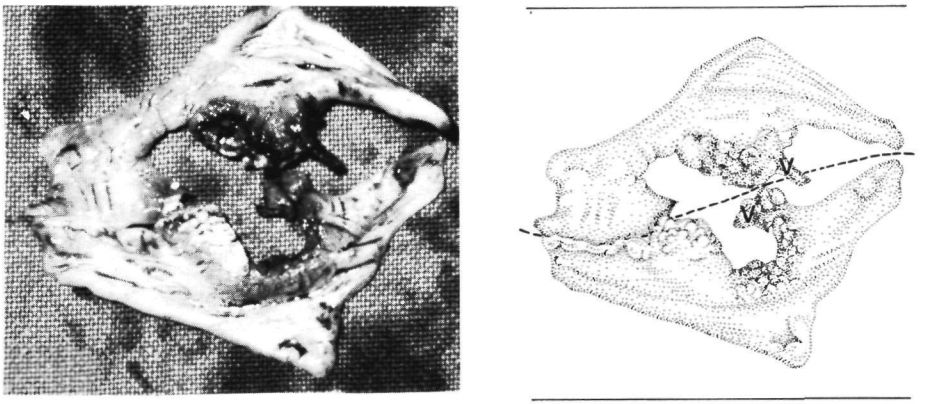


Figure 14. M-mode echocardiogram from case 17, demonstrating diastolic fluttering of the aortic valve leaflets with failure of the leaflets to meet in diastole (arrows). These findings are diagnostic of destruction of valve leaflets.



Surgically removed, bicuspid aortic valve from case 17. Both cusps were partially destroyed by vegetations (V). The dotted line in the schematic drawing indicates the normal line of aortic valve closure.

valve pathology.

A. Native valves

In the 34 patients with native valve pathology 39 valves (and supporting structures) were involved as definitely proven by surgery (25 aortic valves; 11 mitral valves; two pulmonic valves; one tricuspid valve).

a) Vegetations

Excluding the two "false positive" cases (see under mitral valve), 15 of the 25 (60%) native valves containing vegetations were, as such, correctly identified by echocardiography. Distribution of vegetations on valves was as follows.

Aortic valve. Ten of the 16 patients found at surgery to have aortic valve vegetation had positive aortic valve echocardiograms. In six patients with aortic valve vegetations found at surgery, no vegetations were detected by echocardiographic examination ("false negative" echo-findings): in three patients thin diastolic fluttering echoes were seen (in retrospect, in one of these patients with a "rather great" vegetation found at surgery, the gainsettting of the echocardiographic instrument was too low and it was not possible to visualize the entire aortic valve by the echobeam; in two patients only very small vegetations (± 2 mm) were found at surgery, attached to the remnants of the destructed aortic valve leaflets; figure 14 shows the echocardiogram and excised aortic valve from one of these patients); in the other three patients with chronic pre-existing calcified aortic valve disease, it was not possible to differentiate the multiple echoes reflected from these markedly abnormal valves from superimposed vegetation-echoes (see, for example, figure 21). In two patients with large vegetations attached to the ventricular side of the aortic valve, extra echoes were seen in the left ventricular outflow tract.

Mitral valve. Four of the 11 patients with mitral valve pathology were thought to have vegetations on the echocardiogram. In two patients, swollen confluent chordae tendineae (figure 17), respectively a pedunculated myxoma attached to the mitral valve, were thought to represent vegetations. So these represented

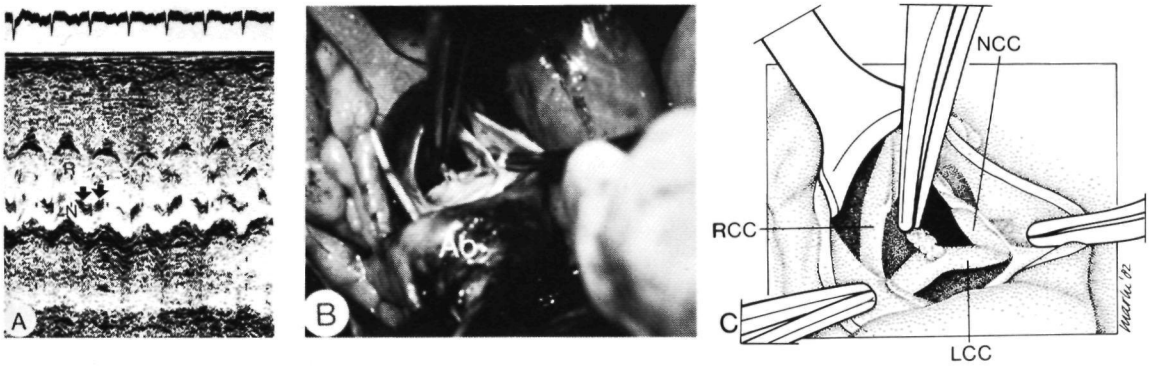


Figure 15. Echocardiogram and operative finding in case 43.
M-mode echocardiogram of the aortic valve (A), showing multiple irregular echoes (arrows) in the region of the aortic valve, indicating a vegetation. The abnormal echoes maintain a mid-aortic position throughout the cardiac cycle, suggesting localization of the vegetation on the left coronary cusp. Operative photograph (B) with schematic drawing (C): forceps holding vegetation, 3 mm in diameter, attached to the edge of the left coronary cusp of the aortic valve (LCC).
Abbreviations: R(CC) = right coronary cusp, N(CC) = non-coronary cusp.

two "false positive" examinations (misinterpretation of abnormal echoes). Echocardiography identified only two of the six patients which were found during surgery to have mitral valve vegetations. Thus there were four "false negative" echo-findings: in the above mentioned patient with ruptured swollen chordae tendineae some very small vegetations appeared to be attached to the edge of the anterior mitral leaflet; in one patient with thick voluminous mitral valves small vegetations on the posterior mitral leaflet were not detected (figure 18); the other two had fibrosed, calcified stenotic mitral valves containing some vegetations (the same interpretation problem as discussed under aortic valve pathology).

Pulnonic valve. In both patients with right-sided endocarditis, vegetations were seen on the posterior pulmonic valve (figure 20).
Tricuspid valve. In one of the patients with right-sided endocarditis, a vegetation on the septal leaflet of the tricuspid valve was detected by echocardiography..
The size of vegetations was not always recorded by the surgeon in his operation report, but the diameter of most vegetations was less than 1 cm. The smallest vegetation detected by echocardiography had a longitudinal diameter of 3 mm and was attached to the left coronary cusp of the aortic valve (figure 15), the largest measure of a vegetation was 4 cm^3 (2 x 2 x 1 cm; figure 27).

b) Destruction/perforation

An indication for destruction of aortic valves in eight of the ten patients was formed by thin, widely separated coarse fluttering diastolic echoes in the aortic root. Extra echoes in the left ventricular outflow tract of two patients indicated a flail (ruptured) aortic valve. The destruction could not be visualized by echocardiography in the other two patients. Only a rupture of the chordae tendineae of the anterior mitral leaflet was diagnosed by echocardiography in one of the patients with mitral valve pathology; a concomitant destructed posterior mitral leaflet was not seen. Perforations of aortic and mitral valve leaflets were not visible; only the sequelae could be demonstrated in the form of a dilated hyperkinetic left ventricle.

c) Deformity, calcification, scarring

Aortic valve deformity was generally caused by bicuspid valves, often with secundary calcification. Seven of the 14 bicuspid aortic valves found at surgery were identified by echocardiography. An abnormal excentricity index of more than 1.3 was seen on the M-mode echocardiogram of only four patients. In the other three patients with a normal midaortic closure point the diagnosis was made by 2D-echocardiography. In seven patients the diagnosis was not made because of: a) difficulty in determining the diastolic closure point caused by widely separating (shrivelled) or flail valve leaflets in three patients and by multiple reflecting echoes from deformed thickened calcified

leaflets in two patients; b) a normal diastolic closure point on the M-mode echocardiogram in two patients (2D-echocardiography not performed). Deformed mitral valves were correctly identified by echocardiography in four patients: three with mitral stenosis; one with thickened anterior and posterior mitral valve leaflets with a prolapse of the posterior mitral valve.

d) Rupture of chordae tendineae

Rupture of the chordae tendineae of the mitral valve was detected by echocardiography in four, and suspected in one, of the seven patients. On the M-mode registration a coarse diastolic fluttering was seen on the anterior mitral leaflet in three, on the posterior leaflet in one. A fine systolic mitral valve fluttering (the most important M-mode feature for chordal rupture) was seen in all four patients (figure 16). A peculiar finding in one of the patients with ruptured chordae tendineae of the anterior mitral leaflet was the occurrence of extra diastolic echoes in the left ventricular outflow tract, caused by swollen confluent chordae tendineae (figure 17).

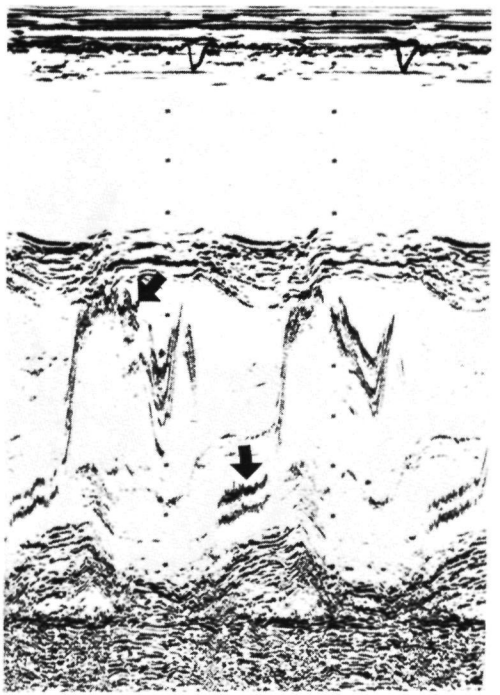


Figure 16. M-mode echocardiogram of the mitral valve from case 37 with ruptured chordae tendineae. Note the coarse diastolic flutter of the anterior mitral leaflet (left arrow) and the fine high-frequency systolic mitral leaflet fluttering (right arrow). Paperspeed was 50 mm/sec.

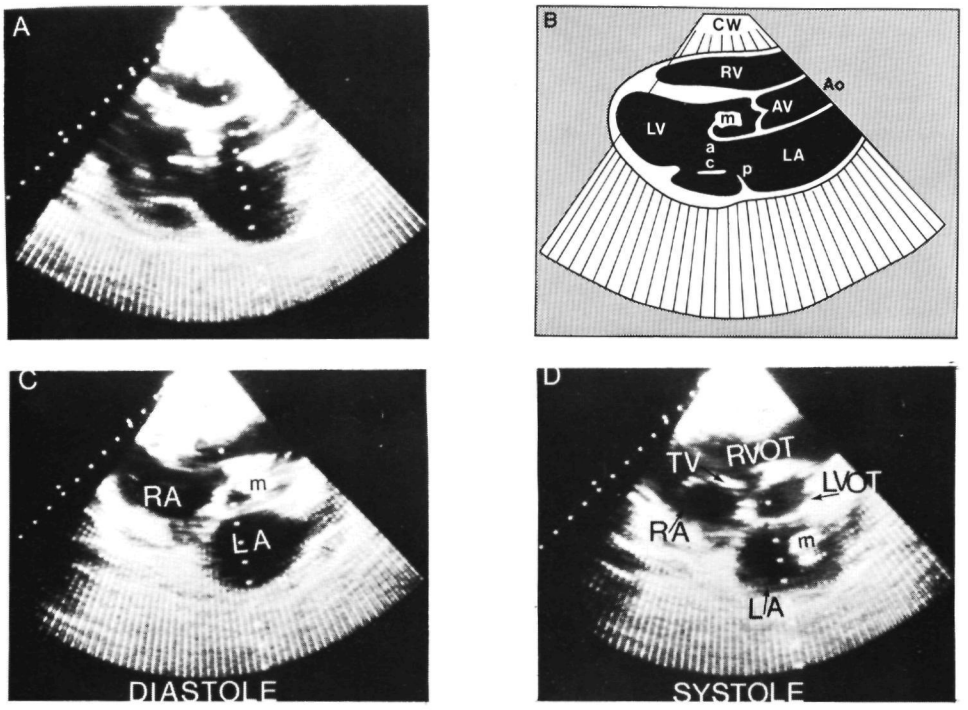
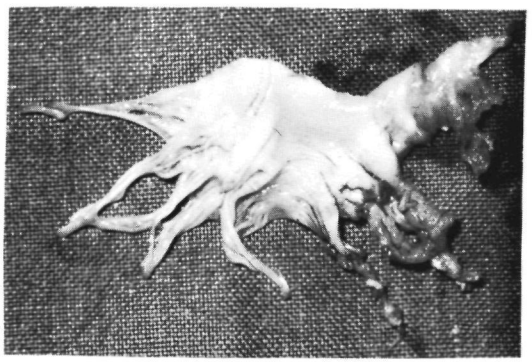


Figure 17. Two-dimensional echocardiograms, and mitral valve obtained at surgery, from case 36 (case history and illustrations are published in Neth. J. Med., 1980 and Chest, 1982). Panel A (with schematic illustration B) is a long-axis two-dimensional echocardiogram. The image is a stop action video frame at mid-diastole representing a 80° scan through aorta (Ao), left atrium (LA), right ventricle (RV), and left ventricle (LV). Note mass of echoes (m) just distal to aortic valve (AV). CW = chest wall; IVS = interventricular septum; a = anterior mitral leaflet; p = posterior mitral leaflet; c = chordae belonging to posterior mitral leaflet. Panels C and D are short-axis two-dimensional echocardiograms, at level just distal to aorta. Panel C is a diastolic stop-frame image: mass of echoes is seen in left ventricular outflow tract (LVOT). Panel D is a systolic stop-frame image: a globular mass of echoes (m) is seen in left atrium (LA). RA = right atrium; RVOT = right ventricular outflow tract; TV = tricuspid valve in closed position.



E. Anterior mitral leaflet (left ventricular aspect) after removal. Chordae tendineae on the left are cut by the surgeon; chordae on right side of photograph were disrupted from papillary muscle. The confluent and swollen chordae tendineae produced the mass of echoes seen by two-dimensional echocardiography.

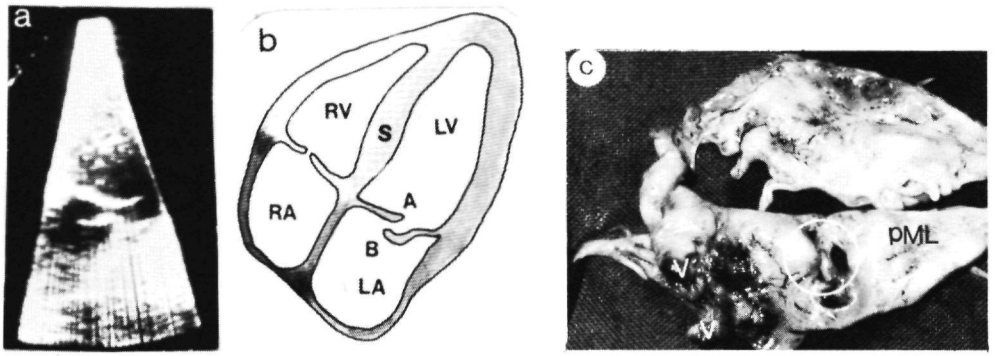


Figure 18. Two-dimensional echocardiogram and pathological specimen of the mitral valve leaflets from a patient with mitral valve prolapse (case 38).
Panel a is a 30° sector scan image, recorded during systole, with transducer in apical position. Panel b is an idealized schematic diagram. Both valve leaflets appear thickened; the posterior mitral leaflet (B) moves beyond the anterior mitral leaflet (A) and beyond the line of mitral closure, into the left atrium (LA). Panel c: surgical specimen of the mitral valve. Both leaflets were thickened and voluminous. The chordae tendineae were intact, but those attached to the posterior mitral leaflet (pML) were elongated. Two perforations were present in the posterior mitral leaflet (white circle), and some small vegetations (v) were noted on the anterolateral portion of the valve.

In a patient with a Carpentier ring in mitral position, chordal rupture was suspected because a coarse diastolic fluttering of the posterior mitral leaflet was visible but an eventual fine systolic fluttering could not be seen due to the multiple reflecting echoes of the Carpentier ring. In two patients the paper-speed was too low (25 mm/sec) to detect the eventual presence of systolic mitral valve fluttering. Two D-echocardiography was not performed in these three patients.

e) Mitral valve prolapse

In one patient with post-rheumatic mitral regurgitation, on 2D-echocardiography a systolic motion toward the left atrium of the posterior mitral leaflet was seen; both leaflets appeared to be thickened. At operation the surgeon noted great voluminous mitral valves; the posterior leaflet could easily be pulled into the left atrium. The chordae belonging to this leaflet were stretched (elongated). In addition a few perforations and vegetations were found (figure 18).

B. Prosthetic valves

Four patients underwent prosthetic valve replacement. In the two patients with Björk-Shiley aortic valvular dehiscence and subsequent aortic insufficiency, no definite abnormal echocardiographic features could be seen, except diastolic fluttering of the anterior mitral leaflet in both patients. Fluoroscopic and cine-angiographic findings of prosthetic valve dehiscence were confirmed at surgery. In the patient with malfunction of the Björk-Shiley prosthetic valve in the mitral position, a characteristic "hump" during the opening phase of the disc was seen on the echocardiogram. This, in combination with a short interval from aortic valve closure to mitral disc opening (45 msec) and signs of left ventricular volume overload, was consistent with significant perivalvular leak. In the patient with the Starr-Edwards cloth-covered mitral prosthesis, the malfunction consisted of a pannus of fibrous material covering the base of the cage, thus producing a stenotic prosthetic orificium. The M-mode echocardiogram from this prosthesis showed the normal anterior and posterior echoes moving parallel and originating from the struts, respectively the base, of the cage. The amplitude of ball movement was 8 mm; its opening-velocity 300 mm/sec; its closing velocity 800 mm/sec (normal values). Because the base of the cage can reflect multiple echoes - even in retrospect - it was not easy to confirm that the multiple echoes seen on the M-mode echocardiogram resulted from the ingrowth of fibrous tissue.
Unfortunately there were no prior recordings - from shortly

after the initial operation - for comparison. In fact the echocardiographic examination did not contribute very much to the diagnosis of impairment of prosthetic function in this patient.

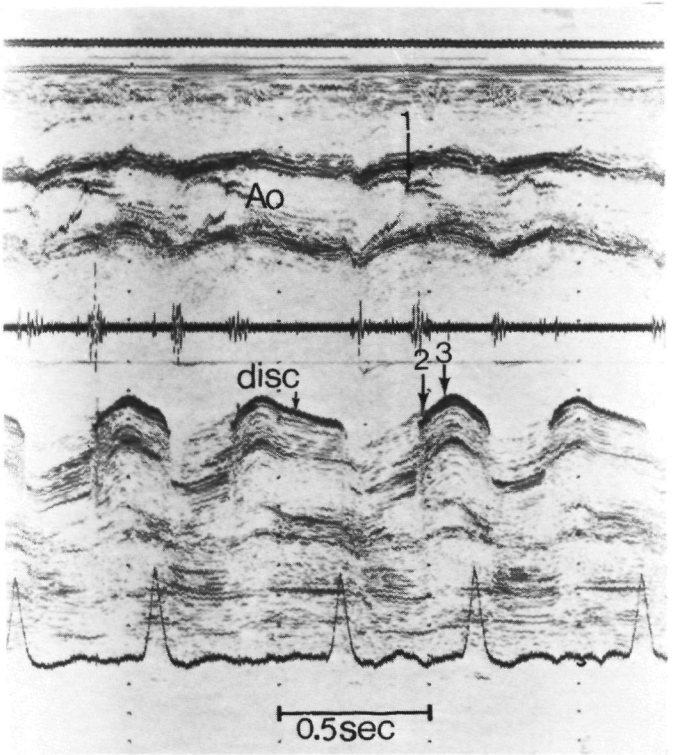


Figure 19. The simultaneous dual M-mode echocardiograms from the aortic valves (top trace) and the disc movement of the Björk-Shiley mitral valve prosthesis (bottom trace) in a patient with severe paravalvular regurgitation (case 39). The time interval from aortic valve closure (arrow 1) to mitral disc opening (arrow 2) was shortened (45 msec). Note the "hump" in early diastole (arrow 3). Paperspeed: 50 mm/sec.

C. Congenital abnormalities

Of the congenital abnormalities (bicuspid aortic valves are discussed ad A.c), only the subpulmonic stenosis (= infundibular pulmonic stenosis) was identified as a band of echoes in the right ventricular outflow tract (2D short axis view) in one

(case 46, figure 20), and a narrowing of the lumen of the RVOT on the M-mode echo in the other. Because of thorax deformity in this last patient, examination was difficult; a subaortic membrane was not seen, but the aortic valves could clearly be identified. Because of extra echoes seen on the left coronary cusp, the aortic valves were inspected by the surgeon. An old vegetation was removed (figure 15). During this procedure a subvalvular membrane was detected and excised. In the other patient with right-sided endocarditis, a small ventricular septal defect was not detected by echocardiography. At surgery the tricuspid valve was carefully inspected because of echocardiographic suspicion of vegetation. Indeed this vegetation was found (and removed); but in addition there was a perforation of the septal leaflet caused by a small ventricular septal defect, type left ventricle to right atrium. In fact it is not quite certain whether this ventricular septal defect was a congenital abnormality or the result of the infective process.

D. Miscellaneous

In the six patients with (partly) necrotic annular tissue this was not diagnosed by echocardiography (quality of tissue cannot be recorded yet). The (old) abscess cavities found at surgery in five patients were not detected by echocardiography in four because they were too small. In the patient with a large aneurysmal cavity extending from interventricular septum into right ventricular outflow tract, this diagnosis was correctly made by 2-dimensional echocardiography (figure 21). In the patient with a ruptured sinus of Valsalva aneurysm into the right atrium, this diagnosis was made because of diastolic fluttering of the tricuspid valves in combination with signs of volume overload of the right ventricle. In addition the dimension of the aortic root was definitely increased, compared with a previous echocardiographic examination. In both patients with right-sided endocarditis multiple erratically moving masses of echoes were seen in the outflow tract of the right ventricle (figure 20).

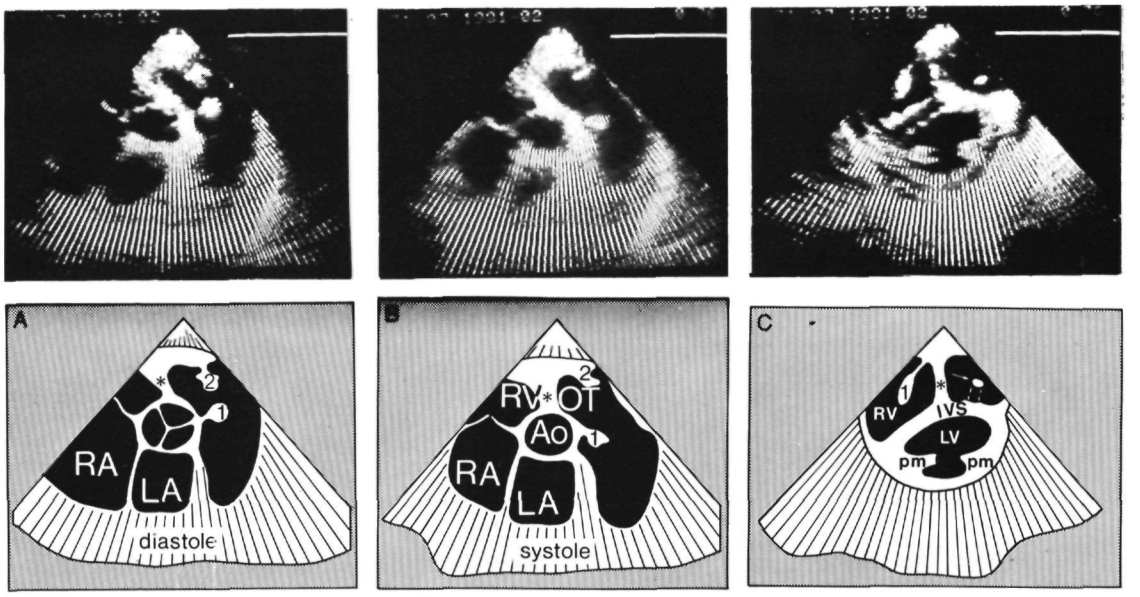
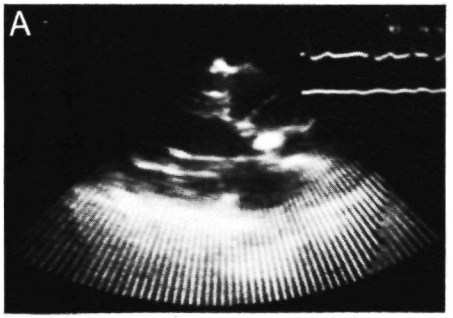


Figure 20. Two-dimensional echocardiograms and operative photograph from case 46, with infundibular pulmonic stenosis and right-sided endocarditis. Each frame is accompanied by a labeled, idealized diagram. Panels A and B are short-axis views at the level of the aortic root (Ao). A globular vegetation (1) is present on the posterior pulmonic valve; an irregular shaped vegetation (2) is attached to the anterior wall of the right ventricular outflow tract (RVOT). Panel C is a short-axis view at the level of the papillary muscles (pm) of the left ventricle (LV). Note the long, pedunculated vegetation (1) in the right ventricle (RV), attached to the anterior wall of the RV, and the cross-section of a smaller one (arrow) attached to the right ventricular side of the interventricular septum (IVS). In panel A, B and C the infundibular pulmonic stenosis can be appreciated as an abnormal structure (asterisk) in the RVOT, extending across the right ventricular cavity. Both findings were confirmed at surgery: The infundibular pulmonic stenosis was caused by anomalous muscle bundles in RVOT; the mural endocardial vegetations were found adjacent to these anomalous muscle bundles; figure D shows valve vegetation.

D. Photograph of opened pulmonary artery showing a large vegetation(V) attached to the posterior cusp (PC) of the pulmonic valve. LC = left cusp; RC = right cusp.



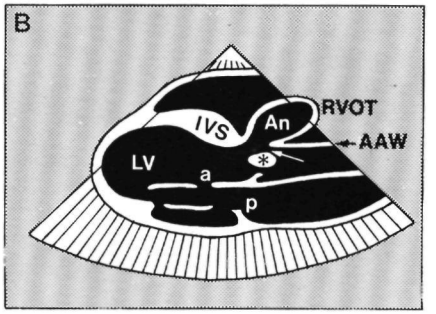
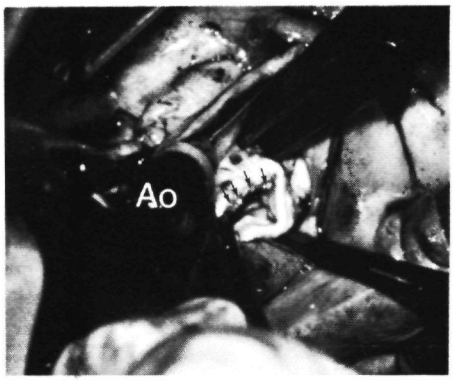


Figure 21. Echocardiogram and operative photograph from case 26, with pre-existent calcific aortic valve stenosis, and aortic regurgitation occurring after IE.

The two-dimensional (long-axis) echocardiogram (A) is accompanied by a labeled, idealized diagram (B). It represents a diastolic stop-frame image: the anterior (a) and posterior (p) mitral leaflets open into the left ventricle (LV), the aortic valve is closed. Dense echoes are obtained from the thickened, calcified, aortic valve leaflets (black asterisk). Superimposed echoes from (surgically detected) vegetations can not be differentiated from the multiple echoes reflected from these markedly abnormal valves. An aneurysm (An) can be seen with the orifice in the proximal part of the interventricular septum (IVS), and extending into the right ventricular outflow tract (RVOT). Note also an interruption of echoes between anterior aortic wall (AAW) and anterior side of the thickened aortic valve (white arrow). At this side the aortic valve was detached from the aortic annulus, thus causing aortic regurgitation.



Operative photograph, showing small vegetations (arrows) on the edge of a bicuspid aortic valve. The base of the right coronary cusp is detached from the aortic annulus; a forceps is placed in the gap. Ao = opened aorta. (After removal of the aortic valve the echo-finding of an aneurysm of the proximal part of the IVS was confirmed; this is not shown on the photograph).

3.2.11.3. Culture and/or microscopic examination of excised specimens (Table 16)

From the 21 patients classified as having "active" endocarditis 29 specimens were obtained (24 native valves, three prosthetic valves, two right ventricular outflow tract vegetations). Twenty-five of these specimens were cultured (nine times alone, 16 times in combination with histologic examination/Gram's staining); 20 specimens underwent histologic examination/Gram's staining (four times alone, 16 times in combination with culture). Nineteen (65.5%) of these 29 specimens showed signs of infection ("positive"): ten times micro-organisms were seen by Gram's stain (in one of these patients the characteristic spores and "mycelium" from the candida albicans were seen by microscopy); seven times histologic active signs of inflammation but without visible micro-organisms; a positive valve culture in one patient (streptococcus faecalis, the same micro-organism as cultured from the blood); a positive valve culture in another patient (streptococcus bovis, a different micro-organism, for E.coli was cultured from the blood), in combination with positive Gram's stain

TABLE 16. Culture and/or microscopic examination of excised material (55 specimens from 46 pts)

Culture (N=40)	Gram's stain (N=39)	Active (N=29)	Healed (N=26)
-	-	7 *	7 **
+	+	1	0
-	+	8	1
+	ND	1	0
ND	+	2	2
ND	-	2 ***	9
-	ND	8	7

ND = Not done (the department of bacteriology or pathology did not receive material).

* At histologic examination 5 x evidence of active infection

** " " " 2 x " " " "

*** " " " 2 x " " " "

Of the other ten specimens, cultures were negative; stain was not done in eight; culture, stain, as well as histologic examination were negative in two.
From the 25 patients classified as having "healed" endocarditis, 26 specimens were obtained (25 native valves, one prosthetic valve). Fifteen of these specimens were cultured (seven times alone, eight times in combination with histologic examination/ Gram's staining); 19 specimens underwent histologic examination/ Gram's staining (11 times alone, eight times in combination with a culture). Only five (19%) specimens were positive: three times micro-organisms were seen by Gram's stain (in specimens obtained respectively 2 weeks, 3.5 months and 3 years after antibiotic treatment for IE); twice histologic examination showed evidence of active inflammation (in specimens obtained respectively 2 months and 2 years, 4 months after antibiotic treatment for IE). From the other 21 specimens in five, the culture, stain and histologic examination were negative; in seven, the culture was negative, stain not done; in nine, culture not done, stain negative. All 15 cultures were negative in this group; hence from the total of 40 cultured specimens only two cultures were postive (5%). From the total of 39 microscopic examinations, 23 (59%) were positive (14 times Gram's stain positive, 9 times histologic evidence of inflammation). Of the total 55 obtained specimens in 24, both culture and stain were done. The results were concordant (culture and stain both + or -) in 15 (62.5%) and discordant (culture negative, stain positive) in 9 (37.5%).

3.2.12. Operative procedures (Table 17)
In the 44 patients who underwent valve replacement, 49 prosthetic valves were implanted. In 29 cases a Björk-Shiley prosthesis was employed, whereas in 20 a bioprosthesis was used (16 Carpentier-Edwards-heterografts, four Ionescu-Shiley pericardial xenografts). Of the prostheses implanted, 29 were in the aortic-, 17 in the mitral- and three in the tricuspid position.
All 26 patients in the "aortic group" underwent isolated aortic

TABLE 17. Prosthetic valve implantation (49 in 44 patients)

	Active pts (N=19)	Healed pts (N=25)	Total pts (N=44)
Aortic position	14	15	29
Mitral position	7	10	17
Tricuspid position	2	1	3
Total prostheses	23	26	49
Björk-Shiley	13	16	29
a) before 1978	9	13	
b) since 1978	4	3	
Bioprosthesis (since 1978)	10	10	20

valve replacement (15 times, Björk-Shiley; nine times, Carpentier-Edwards; twice, Ionescu-Shiley).

All 13 patients in the "mitral group" underwent isolated mitral valve replacement (nine times, Björk-Shiley; four times, Carpentier-Edwards). Five out of seven patients in the "mixed group" underwent valve replacement. Isolated tricuspid valve replacement (Björk-Shiley) was performed once; a double valve replacement was performed on three occasions (mitral and tricuspid valves were replaced by Björk-Shiley prostheses in one patient; aortic and mitral valves were replaced by Björk-Shiley prostheses in another patient; and aortic and mitral valves were replaced by Ionescu-Shiley prostheses in still another case); and triple valve replacement in one patient (aortic, mitral and tricuspid valve replaced by Ionescu-Shiley prostheses). Twenty-three prostheses were implanted in the "active" patient group (13 times, Björk-Shiley; ten times, bioprostheses) and 26 in the "healed" patient group (16 times, Björk-Shiley, ten times bioprostheses). In the period 1972-1978 only Björk-Shiley prostheses were implanted. Since 1978 mostly biopros-

theses were used, in the "active" patient group as well as in the "healed" patient group. Björk-Shiley valves were only used when the diameter of the aorta was small (three times) or in case of replacement of prosthetic material (four times).
Associated surgical problems and/or procedures were:

a) Annulus involvement. In the six patients with (partly) necrotic valve rings (four patients with native valve IE, two patients with prosthetic valve IE), the areas of necrotic tissue were debrided as thoroughly as possible by the surgeon. The sutures were buttressed with synthetic material (Teflon pledgets) due to poor quality of the tissue. Despite these precautions, severe postoperative periprosthetic leaks occurred in three patients; all three ultimately died after re-operation, see 3.2.13.1.
b) Old abscess cavities (deep erosions) with orifices just below the aortic annulus in five patients were debrided and obliterated by sutures.
c) Aneurysm of sinus of Valsalva. In the patient with aneurysm of the sinus of Valsalva, ruptured into the right atrium, repair was performed by partial resection of the aneurysm and closure of the aortic opening. The same sutures were used to secure the prosthetic valve.
d) Dissecting aneurysm. In the patient with a dissecting aneurysm of the aorta ascendens a Meadox Cooley dacron interpostion was done.
e) Atrial septal defect of the secundum type was closed with a running suture.
f) Ventricular septal defect. In one of the patients with right-sided endocarditis a small ventricular septal defect with left ventricle to right atrium communication was closed with interrupted sutures.
g) Removal of vegetations. In the two patients with right-sided endocarditis, vegetations in the right ventricular outflow tract and on pulmonic- and tricuspid valves were removed. In addition, in one of the patients an old vegetation was removed from one of the aortic cusps.

h) Partial resection of structures/valves. In one of the patients with right-sided endocarditis and subpulmonic stenosis, part of the hypertrophic crista supraventricularis was removed and a pericardial patch was used to widen the infundibulum of the right ventricle. In addition, a small subvalvular aortic membrane was removed in this patient.
In the other patient with subpulmonic stenosis caused by anomalous muscle bundles in the right ventricular outflow tract, this anomalous tissue was excised. In addition the posterior pulmonic valve, containing a large vegetation, had to be removed in this patient.

i) Tricuspid regurgitation. In patients requiring mitral valve replacement a concomitant moderate tricuspid valve regurgitation was corrected by an annuloplasty according to Kay.

3.2.13. Operative results (Table 18)

Eleven of the 46 operated patients died (24%). There were seven hospital deaths, and four late deaths. Eight of the 21 patients with "active" endocarditis died (38%: six hospital and two late deaths) and three of the 25 patients with "healed" endocarditis died (12%: one hospital and two late deaths). In these last three patients, the time interval between completion of antibiotic therapy for IE and operation, was rather short: respectively 3 weeks, 5 weeks and 2 months.

TABLE 18. Causes of death after surgery

Causes of death	NV	PV	Case no.	Time after surgery
1. Hospital death (N=7) (<6 wks after operation)				
			A A H ↓ ↓ ↓	
Arrhytmia	3x		3,9,4	1 month, 10days,6hours
Cerebral		1x	8(A)	2 days
Multiple (cardiac,pulmonary, renal,cerebral)	2x	1x	11,14,39 ↑ ↑ ↑ A A A	2.5wks,6wks,3wks
2. Late death (N=4)			A H H ↓ ↓ ↓	
Prosthetic valve dehiscence			12, 7, 25	7.5-,7-and 3 months
Overdose i.v. Heroin			23 ↑ A	5 months

NV = Native valve
PV = Prosthetic valve
A = Patient belonging to "active group"
H = Patient belonging to "healed group"

3.2.13.1. Case histories of the patients who died

The description of the following case histories is a rather detailed one, in order to illustrate how acute/chronic/complicated/treacherous (and ultimately fatal) the course of IE can be.

Case 3 (A.V., 33 years at operation). In July, 1972, he was treated for 1 month with penicillin intravenously for a streptococcus viridans endocarditis. In March, 1973, he was admitted to our hospital because of fever and progressive tiredness. Physical examination revealed aortic regurgitation with evidence of heart failure. Blood culture showed beta-hemolytic streptococcus group A. The patient was started on intravenous antibiotics (penicillin)

with a prompt normalisation of his temperature. Heart failure was treated with digitalis and (daily) diuretics. However, at the end of the antibiotic course his temperature rose again and then candida albicans was cultured from his blood. He was treated with amphotericin B in combination with 5-Fluorocytosine during 1 month. Because of persisting elevation of temperature and moderate heart failure due to aortic regurgitation, he was operated upon. Upon surgery (May 11, 1973) a trileaflet aortic valve was found (figure 22). The right cusp was covered with a bulky polypoid like vegetation, the non-coronary cusp was perforated. Part of the aortic annulus was necrotic at the right coronary cusp-side and necrotic tissue (abscess) was found in the proximal part of the interventricular septum. The necrotic tissue was debrided with a curette. The aorta ascendens and the left ventricle were irrigated with amphotericin solution and subsequently a Björk-Shiley prosthesis was inserted with extra matras-sutures on dacron at the side of the right coronary cusp through the proximal part of the interventricular septum. Despite adequate antibiotic treatment (ampiclox, respectively chlooramfenicol and erythromycin in combination with amphotericin), he had persistent fever and a pericardial friction rub was heard 2 weeks after the operation. The electrocardiogram at that time showed a QRS complex of 0.08 seconds, electrical axis 0°. On June 4, the QRS complex was 0.10 seconds, electrical axis -40° (left anterior hemiblock). On June 10, 1973, early in the morning, he suffered a cardiac arrest. The electrocardiogram made a few minutes after beginning of cardiopulmonary resuscitation showed a straight-line tracing. Resuscitation was tried during 30 minutes, but was unsuccessful.

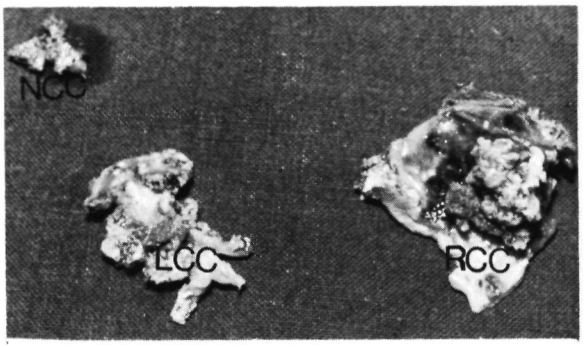


Figure 22. Fungal aortic valve vegetations. RCC = right coronary cusp; LCC = left coronary cusp; NCC = remnant of non-coronary cusp.

Autopsy: pericarditis serofibrinosa; hypertrophic, dilated heart, abscess in interventricular septum with subendocardial penetration to the conus arteriosus (outflow portion of the right ventricle). Dissecting aneurysm of the aortic root, just above the Björk-Shiley valve, with organized thrombus. All sutures of the prosthetic valve were intact.
Microscopic examination: signs of myocardial necrosis with eosinophil degeneration and Karyorhexis of leukocytes (probably due to amphotericin). The material was examined for mycelium, but no signs of candida infection were found.
Comment: patient with fungal endocarditis occurring during antibiotic therapy for beta-streptococcus endocarditis. Fungal vegetations causing destruction and perforation of aortic cusps, necrosis of the aortic annulus and formation of myocardial abscesses. Abscess in interventricular septum penetrating to conus arteriosus may have caused complete heart block and asystole.

Case 4 (v.H., 23 years at operation). This patient who had never been ill in the past, was admitted to a hospital in April, 1976, because of fever, shaking chills, and left abdominal pain. Examination revealed a grade 2/6 ejection murmur over the aortic area and a grade 2/6 aortic regurgitation murmur. A splinter hemorrhage was found under the nail of his left ring-finger. The spleen was enlarged, palpation was painful. A spleeninfarction was documented by scintigraphy. Blood cultures were positive for streptococcus viridans. He was treated with penicillin intravenously during 5 weeks in combination with streptomycin intramuscularly during the first 2 weeks of treatment. Ten days after termination of antibiotic therapy he was discharged from the hospital. One week later he re-entered the hospital because of sudden deterioration. There were signs of left heart failure and a very loud cardiac murmur was heard,interpreted as being systolic. He was transferred to the St. Radboud Hospital on July 14, 1976. At examination he was pale and tachypnoic. Capillary pulse and Duroziez sign were positive. At the left lower sternal border a grade 4/6 diastolic murmur was heard. At the apex the first heartsound intensity was decreased and a short middiastolic murmur was heard. Blood cultures were sterile. M-mode echocardiography (fig.23) demonstrated a dilated, hyperkinetic left ventricle. The mitral valve closure was premature, consistent with severe aortic regurgitation. During

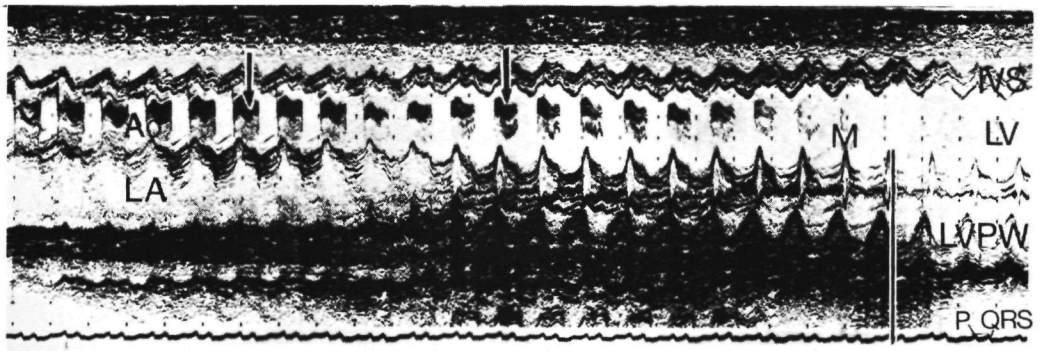
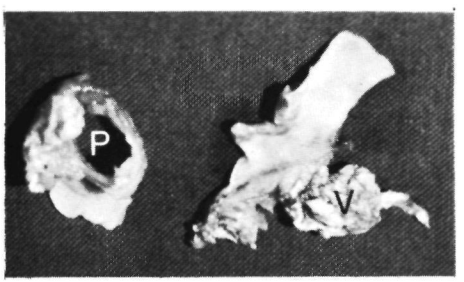


Figure 23. M-mode echocardiogram showing vegetation attached to the aortic valve (left arrow) and prolapsing into the left ventricular outflow tract during diastole (right arrow). Note dilated hyperkinetic left ventricle (LV) and premature closure of mitral valve (vertical line). Figure 6 shows the schematic presentation of this echocardiogram. Ao = aorta; LA = left atrium; IVS = interventricular septum; LVPW = left ventricular posterior wall; M = mitral valve.



Bicuspid aortic valve after removal. Perforation in one valve, vegetation attached to the other valve.

diastole markedly thickened irregular echoes were seen in the aortic root and in the left ventricular outflow tract. Aortic valve motion in systole was preserved. Chest X-ray demonstrated an enlarged heart with upperlobe pulmonary venous distension. Swan-Ganz catheterization revealed a mean pulmonary wedge pressure of 30 mmHg, a pulmonary artery pressure of 70/40 mmHg; the cardiac output was 2.7 l/min, cardiac index 1.7 l/min/m^2. On the base of the above data and his bad general condition he was taken to the operation room one day after admission and without prior left heart catheterization. He experienced a cardiac asystole during skin incision. The thoracotomy was rapidly carried out and internal cardiac massage was performed during 20

minutes until cardiopulmonary bypass was instituted. A bicuspid aortic valve was found with a one cm perforation in the largest aortic valve, and a vegetation approximately 1 cm in diameter on the other valve (figure 23). The valves were replaced by a Björk-Shiley prosthesis. Circulation had to be supported by intra-aortic balloon pump. A few hours after surgery, dangerous ventricular and supraventricular arrhythmias occurred, during which the intra-aortic balloon pump could not function well. Despite high doses of lidocain, pronestyl, ritmoforin and bretylium tosylate these arrhythmias were not sufficiently suppressed. The patient suffered a cardiac arrest, caused by ventricular fibrillation. External cardiopulmonary resuscitation was unsuccessful. He died 6 hours after surgery. Permission for autopsy was not granted.
Comment: patient with severe aortic regurgitation occurring 2 weeks after completion of a full course of antibiotic treatment because of streptococcus viridans endocarditis. At operation he was in a bad general condition with a low cardiac output syndrome. He died 6 hours after operation with intractable ventricular and supra-ventricular arrhythmias.

Case 7 (S.v.V., 33 years at operation). This patient was admitted to a hospital in September, 1976, because of a painful and swollen left underarm. At examination his temperature was 38.4°C and a cardiac systolic and diastolic murmur was heard by the internist. He thought the swollen left arm to be caused by a thromboflebitis. Blood cultures showed streptococcus viridans and the patient was treated with penicillin and streptomycin parenteral. On October 9, he suddenly became dyspneic, on chest X-ray the heart was enlarged with signs of pulmonary congestion. He was treated with digitalis and diuretics, with some improvement. Because of persisting pain in his left arm and signs of severe aortic regurgitation he was referred to the St. Radboud Hospital on November 8, 1976. On examination he was somewhat pale and slightly dyspneic. Blood pressure 145/60-0 mmHg with bounding arterial pulses. Capillary pulse and Duroziez sign were positive. Auscultation: aortic regurgitation murmur 3/6, reduced intensity of the first heart sound and middiastolic rumble at the apical region. The left underam was red and swollen. At arteriography a mycotic aneurysm of the left arteria ulnaris was demonstrated. The M-mode echocardiogram revealed a dilated hyperkinetic left ventricle. There was a diastolic fluttering of the anterior mitral leaflet and the mitral valve closed at the beginning of the QRS-complex.

The systolic movement of the aortic valve was not restricted. The right coronary cusp was thickened. During diastole multiple shaggy echoes were seen in the middle of the aortic root. One day after admission the aneurysm of the left arteria ulnaris was ligated. One week after this operation the antibiotic treatment was stopped and the temperature remained normal. Despite digitalis and diuretics he remained dyspneic on slight exertion. M-mode echocardiography demonstrated extra echoes on the anterior aortic leaflet (as seen in systole) and multiple irregular diastolic echoes in the midposition of the aortic root. The left ventricle was dilated with hyperkinetic movement of septum and posterior wall. At catheterization of the right heartside the mean pulmonary wedge pressure was 29 mmHg, pulmonary artery pressure 50/23 mmHg. At surgery (December 6, 1976) a trileaflet aortic valve was found with small vegetations on all the leaflets; the largest vegetation was attached on the right coronary cusp; the other 2 cusps were partly destructed. The aortic annulus was partly necrotic. The aortic valve was replaced by a Björk-Shiley prosthesis. A few days after operation a diastolic murmur grade 2/6 was heard left parasternal. There were no signs of heart failure. Twelve days after surgery he was discharged in good condition. Six and a half months after operation he had to be readmitted because of complaints of increasing dyspnea on exertion. The aortic regurgitation murmur was definitely louder. Cinefluoroscopy documented a marked tilting of the ring of the prosthetic valve compared to the cineröntgenfilm just after the operation (figure 24). One week later he was re-operated· the sewing ring was partly displaced from the aortic root because of disruption of half of the sutures. The aortic annulus at the place of the loosened prosthesis contained granulation tissue. This tissue and the prosthesis were excised and a new Björk-Shiley prosthesis was inserted. Postoperative an aortic regurgitation murmur was heard again. Two weeks after operation he was discharged from the hospital. Two days after dismissal he was re-admitted in cardiogenic shock. He died a few hours later. At autopsy the prosthetic valve appeared to be nearly completely disrupted from the aortic root (only 4 sutures were intact). There were signs of inflammation of the aortic annulus and -root.

Comment. this patient underwent an aortic valve prosthesis operation 3 weeks after completion of an antibiotic course for streptococcus viridans endocarditis. On account of a necrotic aortic annulus, a postoperative periprosthetic leak occurred and he had to be re-operated half a year after the first

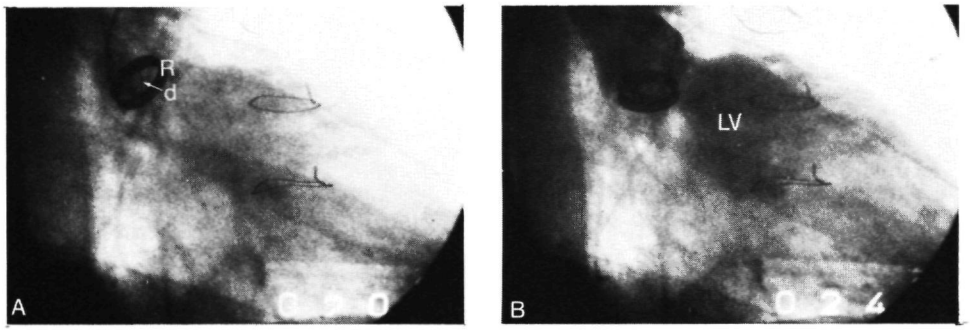


Figure 24. Aortogram demonstrating regurgitation of contrast material into left ventricle (LV) and a marked tilting (30^{o}) of the ring (R) of the Björk-Shiley aortic valve prosthesis. A = systolic frame (note radiopaque disc, d, in opened position); B = diastolic frame (d in closed position).

operation. At this operation part of the aortic annulus contained granulation tissue. He died 2 weeks after this operation because the re-implanted Björk-Shiley prosthesis had detached nearly completely.

Case 8 (F.S., 66 years at operation). He received an aortic valve Björk-Shiley prosthesis in 1975 in another hospital because of severe (rheumatic) aortic regurgitation. On March 16, 1977, he was admitted to our hospital with high fever, headache, mental aberration and weakness in right arm and leg. Upon cardiac examination normal prosthesis opening and closing clicks were heard. A grade 1/6 aortic regurgitation murmur was present. Neurologic examination revealed a bradyphrenic, aphasic man with desorientation in time, place and person. He had a mild right hemiparesis. The fluid obtained by lumbar puncture was slightly turbid with a somewhat increased protein content; the sediment of the spinal fluid contained some lymphocytes and polymorfonuclear cells. Gram's stain for bacteria was negative. Blood cultures showed diphteroids. Parenteral penicillin in combination with cloxacyllin and gentamycin was administered. Despite these measures fever persisted. An electro-encephalogram showed focal abnormalities in the left hemisphere. Carotid arteriography revealed diffuse arteriosclerotic lesions in both arteriae carotides and an occluded left middle cerebral artery. During antibiotic treatment the aortic regurgitation murmur became definitely louder. There were no signs, however, of left heart failure. On the M-mode echocardiogram a fine diastolic fluttering of the anterior mitral leaflet was seen. The left ventricle dimension was normal. On cinefluoroscopy the

prosthetic valve movement was increased compared with an earlier examination. Because of persisting fever, in combination with increasing aortic regurgitation and neurological signs of embolism, he underwent cardiac surgery on May, 9, 1977. The aortic valve prosthesis had been partly dehisced from the aortic root because of disruption of one-third of the sutures. At the left ventricular side of the prosthesis old thrombotic material was found. In addition, a small cavity was seen in the proximal interventricular septum. The original prosthesis was excised and a new Björk-Shiley prosthesis inserted. His cardiac situation after surgery was good but the neurologic condition deteriorated with signs of Cheyne-Stokes respiration, bilateral wide pupils without reaction to light, bilateral Babinsky sign. An electro-encephalogram was iso-electric. He died one day after operation. Postmortal examination showed extensive cerebral edema and diffuse small septic embolies; in addition a large hemorrhagic infarction was found in the left frontal lobe.
Comment: infective endocarditis 2 years after Björk-Shiley aortic valve implantation with neurological complications as presenting features of this disease. He underwent cardiac re-operation because of dehiscence of the aortic prosthesis, persisting fever and systemic embolism. Cause of death was an extensive cerebral infarction.

Case 9 (G.T., 27 years at operation). Because of fever, general malaise, arthralgia with swollen knees and ankles he was admitted on August 4, to a department of internal medicine at another hospital. His temperature was 38°C. Physical examination revealed the murmur of aortic regurgitation. Blood cultures were negative. Treatment followed with ascal. After 10 days his temperature suddenly rose to 39°, and he became dyspneic. The murmur was definitely louder and the heart was enlarged on the chest X-ray. He was immediately referred to our hospital and the physical examination revealed severe aortic regurgitation with evidence of heart failure.
The M-mode echocardiogram demonstrated a coarse fluttering of widely separated aortic valve leaflets during diastole. The left ventricle was dilated with hyperkinetic movement of septum and posterior wall.
Despite negative blood cultures the patient was treated for presumed infective endocarditis with intravenous antibiotics (penicillin + gentamycin). Because of severe aortic regurgitation and persistent fever operation followed (August 22, 1977). A bicuspid aortic valve was found, both valves were destroyed and contained small vegetations. After removal of the remnants of the aortic valve a small cavity was seen, located under the non-coronary cusp in the atrioventricular part of the membranous septum just

near the attachment of the anterior mitral leaflet. A Björk-Shiley prosthesis was implanted and the abscess cavity was closed. The postoperative course was uneventful. The temperature fell quickly to a normal level during penicillin and gentamycin treatment. His rhythm was monitored until one week after operation: no arrhythmias were detected. The electrocardiogram just before operation showed a QRS-complex of 0.08 seconds, electrical axis -20^{o}. After operation the QRS-complex was 0.11 seconds, right bundle branch block configuration, axis -35^{o} (left anterior hemiblock). On a routine control by the nurse in the night of September 1, 1977, he was found dead in bed. No resuscitation efforts were undertaken.
Autopsy: dilatation of the heart, correctly implanted aortic prosthesis, normal coronary system, no myocardial infarction. At microscopic examination subendocardial fibrosis was seen with vacuolar dystrophia. Eventual abnormalities in the membranous part of the interventricular septum were not mentioned in the autopsy report.
Comment: patient with aortic valve endocarditis and sterile blood cultures. He died unexpectedly 10 days after aortic valve replacement. Cause of death probably arrythmia (heralded by bifascicular bundle branch block).

Case 11 (G.B., 23 years at operation). This patient was known to have hypertension, a congenital cystic kidney and agenesis of the other kidney. He was seen in March, 1977, at our department because of a murmur. At auscultation of the heart a systolic ejection murmur grade 2/6 and an aortic regurgitation murmur grade 2/6 were heard. On chest X-ray the heart was not enlarged (fig. 25a) M-mode echocardiography (fig. 25b) demonstrated thin aortic valves with normal systolic separation but with an excentric position of the diastolic closure line the valve within the aorta (excentricity index 2.2). It was concluded that he had a bicuspid aortic valve without signs of stenosis, in combination with a slight aortic regurgitation. September 12, 1977, he was admitted to another hospital, to the department of internal medicine, because of a one week history of fever, chills, fatigue and a painful neck. On admission the temperature was $40^{o}C$. The Kernig-sign was positive. There was no change in the character of the murmurs. A blood culture was positive: streptococcus viridans. A lumbar puncture was performed by the neurologist. Culture of the spinal fluid was negative, the stained smear did not contain microorganisms. Despite these negative findings it was concluded that the patient had a subacute meningitis. He was discharged from the hospital after 2 weeks

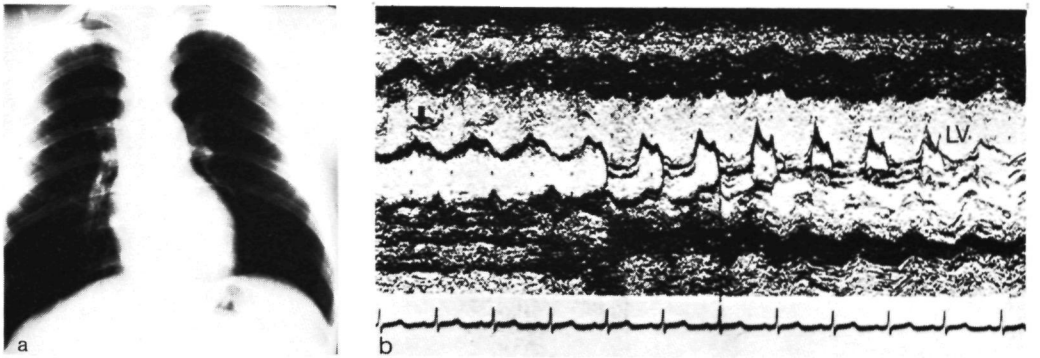


Figure 25. a. Chest X-ray, March, 1977. The heart is not enlarged, normal pattern of pulmonary vascularity.

b. M-mode echocardiogram, March, 1977. Aortic valve leaflets are not thickened. Excentric position of the diastolic closure line of the aortic valve (arrow), indicating bicuspid aortic valve. Normal dimension of left ventricle (LV), normal mitral valve closure (broken vertical line).

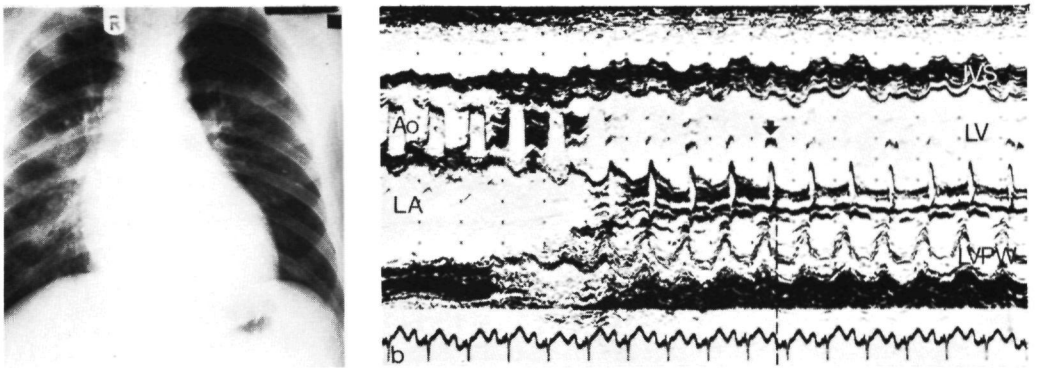


Figure 26. a. Chest X-ray, January, 1978. Note the marked cardiomegaly and the changes of interstitial edema.

b. M-mode echocardiogram, February, 1978. Vegetation on aortic valve (left arrow), prolapsing into left ventricular outflow tract (right arrow). Dilated left ventricle with premature closure of mitral leaflets (broken vertical line), indicating severe aortic regurgitation of recent onset. Abbreviations as in figure 23.

of oral ampicillin. On January 15, 1978, a second admission followed in the same hospital because of progressive dyspnea and fever with shaking chills. A few days before admission ampicillin was prescribed by the general physician. Physical examination revealed a blood pressure of 120/60 mmHg with bounding arterial pulses; the character of the diastolic murmur had definitely changed. On chest X-ray the heart was larger with signs of pulmonary congestion (fig.26a). In the right costophrenic sulcus pleural fluid had accumulated and densities seen on the right side were interpreted as lobular pneumonia. The pulmonologist performed a pleural puncture on the right side. Culture of the fluid was negative, no micro-organisms were seen. Repeated blood cultures were sterile. He was treated with clamoxyl, ampiclox, garamycin and penicillin, streptomycin parenteral. In addition the congestive heart failure was treated with digitalis and diuretics. Despite these measures the patient did not do well: he was orthopneic, the heart remained enlarged on chest X-ray with pulmonary congestion. Therefore he was referred to the St. Radboud Hospital for further investigation. On admission (February 28, 1978) he was lethargic and tachypneic, sitting upright in bed,with a blood pressure of 120/60-0 mmHg. Homo pulsans. Capillary pulse and Durozziez murmur were positive. A grade 3/6 aortic regurgitation murmur was heard. Chest X-ray demonstrated a markedly enlarged heart with evidence of interstitial pulmonary edema; pleural effusion was evident, predominantly on the right side. M-mode echocardiography (fig.26b) revealed a dilated left ventricle without hyperkinetic movement of septum and posterior wall. There was an early closure of the mitral leaflets. The aortic valve motion in systole was preserved, in diastole, markedly thickened irregular echoes were seen prolapsing into the left ventricular outflow tract. This was a distinct change from the M-mode echocardiogram made 1 year before. On the day of admission a right-sided pleural puncture was repeated. The puncture was complicated by a pneumothorax, treated with pleural drainage. Microscopic examination of the Gram's stained preparation did not reveal micro-organisms, culture of the fluid was negative. At catheterization of the right side of the heart the cardiac output appeared to be 2.2 l/min, cardiac index 1.2 l/min/m^2 (Fick method). At surgery 6 days after admission a bicuspid aortic valve was found with a large vegetation attached on one valve and a perforation in the other valve. The aortic annulus was of good quality. An aortic Björk-Shiley prosthesis was implanted. Postoperative he received penicillin and

ceporacin intravenously. The chest X-ray days after operation revealed an infiltrate involving the right lower lobe. Pleural fluid collected from the right pleural drain was purulent. The culture of the pus showed Klebsiella pneumoniae, enterobacter aerogenes and streptococcus faecalis. Bactrimel and gentamycin, later myconasol and globenicol, were added to the antibiotic regimen. Despite these measures the infiltrative lesions on the chest X-ray increased. Sometimes bleeding, pulmono-pleural fistulas developed and the patient died in a septic shock on March 20, 1978. Permission for autopsy was not granted.
Comment: in September 1977, this patient - with known bicuspid aortic valve - suffered IE. This misjudged IE was inadequately treated with antibiotic medication. Three months later he was re-admitted with severe heart failure (due to perforation of one of the aortic valve cusps) and a second (culture negative) IE. After a too long hospitalization period the patient was operated upon in a very bad general condition with low cardiac output due to severe aortic regurgitation. He died because of bronchopneumonia with empyema and pulmono-pleural fistula, enhanced by the pleural punction.

Case 12 (M.v.d.W., 54 years at operation). He was known to us since 1971 with a mild aortic stenosis and insufficiency. He was admitted to our hospital on March 21, 1978, because of fever, general malaise and the occurrence of dyspnea. Physical examination revealed a blood pressure of 120/70 mmHg, temperature 38.6^{o}C. Capillary pulse and Duroziez sign were positive. At auscultation a grade 2/6 systolic ejection murmur and a grade 3/6 aortic regurgitation murmur were heard. The diastolic murmur was definitely louder compared to 1 year before during a control visit. Three blood cultures demonstrated streptococcus viridans and the patient was treated with penicillin intravenously and streptomycin intramuscularly. One week after start of treatment he became suddenly dyspneic. A continuous murmur was heard now, grade 4/6,left parasternal. The chest X-ray showed enlargement of the heart compared to the X-ray at admission, with interstitial pulmonary edema. The M-mode echocardiogram revealed a dilated hyperkinetic left ventricle. The mitral valve closure was premature suggesting severe aortic regurgitation. The aortic root was dilated with an enddiastolic dimension of 4.8 cm. During diastole multiple echoes were seen on the non-coronary cusp and in the left ventricular outflow tract. The right coronary cusp could not clearly be identified. This was a distinct change from the previous echocardio-

graphic study in 1977: at that time a bicuspid aortic valve was diagnosed based on excentric displacement of the diastolic closure point of aortic valves; the aortic root dimension (3.5 cm), left ventricular dimension and mitral valve closure point were normal.

At cardiac catheterization the pulmonary artery pressure was 60/20 mmHg (O_2 saturation 83%); right atrium 10/0 mmHg (O_2 saturation 79%); the O_2 saturation in vena cava superior was 43%. The lung circulation was 3.5 x the systemic circulation. So there was a considerable left-right shunt. The aortic pressure was 100/35 mmHg. Supravalvular aortography showed aortic regurgitation grade 4+. The sinus of Valsalva had an aneurysmatic dilatation on the non-coronary cusp side, contrast was leaking to the right atrium.

The patient was operated on the next day (April 1, 1978): left coronary and non-coronary cusp were fused together and calcified, a vegetation was attached to the non-coronary cusp. The right coronary cusp was completely destroyed. The bicuspid valve was excised. The aortic annulus on the right coronary side was of bad quality causing problems with suturing the Björk-Shiley prosthesis. Some sutures at the right coronary cusp side had to be placed in the proximal part of the septum. The opening between non-coronary cusp and right atrium was closed, using tevdek sutures on teflon buttons.

One day after operation an aortic regurgitation murmur grade 2/6 was heard. On the echocardiogram the left ventricle was still dilated and hyperkinetic. The anterior mitral leaflet showed fine diastolic fluttering. At fluoroscopy there was no abnormal excursion of the valve ring. Supravalvular aortography showed aortic regurgitation grade 3+.Re-operation at the same day followed. Sutures of sewing ring at the right coronary cusp side were loosened. The prosthesis was removed and a new Björk-Shiley prosthesis sutured in place. In order to reinforce suture lines bolstering mattress sutures with double velour dacron material were used on right coronary cusp side. Five days after this operation an aortic regurgitation murmur was heard again. Capillary pulse and Duroziez sign were negative. Because of the stable hemodynamic situation we saw no indication for a third operation. He was discharged from the hospital one month after the last operation. Two weeks later he was re-admitted because of supraventricular tachycardia and severe anemia. The anemia was the result of hemolysis. After infusion of blood and anti-arrhythmic treatment, anemia and rhythm were corrected.

He was discharged after 1 week but had to undergo blood transfusions every three weeks because of the hemolysis with subsequent anemia. On September

11, 1978, he was admitted again to our hospital because of progressive dyspnea. The aortic regurgitation murmur was louder, capillary pulse and Durozíez sign were positive now. Supravalvular aortography showed a periprosthetic aortic regurgitation grade 3+. Again the deformity of the sinus of Valsalva on the right side was seen. Despite apresolin, digitalis and diuretics his situation did not improve.

On November 10, 1978, he was re-operated by Cooley (Houston) who stated: "The Björk-Shiley aortic valve prosthesis was found to be partially detached and was removed. Because of the extensiveness of the aortic annulus involvement and adhesions around the aortic root from the previous 2 procedures an ascending aortic conduit consisting of a 26 mm low porosity graft containing Cooley-Cutter aortic valve prosthesis was inserted. The ostia of left and right coronary artery was closed and double aortocoronary artery bypass grafts were anastomosed to the proximal right and left main coronary arteries and anastomosed to the ascending aortic conduit distal to the prosthetic valve. Difficulties were encountered in attempting to wean him from cardiopulmonary bypass and increasing pharmacologic support was utilized, to no avail. Therefore an intra-aortic balloon pump was inserted via right common femoral artery and advanced into descending thoracic aorta just distal to the origin of the subclavian artery. Actuation of the balloon improved his circulatory status somewhat but the response was inadequate to support circulation. Multiple attempts to wean him from cardiopulmonary bypass were not successful and the patient died. At autopsy the left heart was hypertrophic and dilated. The ascending aortic conduit containing the Cooley-Cutter valve was intact and the saphenous vein grafts to the right and left main coronary arteries were patent. There was extensive calcification in the native aortic valve annulus". The drawing in chapter 2 (fig. 1f) illustrates the surgical technique.

Comment: streptococcus viridans endocarditis causing destruction of one of the bicuspid aortic valves, necrosis of part of the aortic annulus, aneurysm formation of a sinus of Valsalva with rupture into the right atrium. The day after aortic valve replacement by a prosthesis re-operation was necessary because of severe periprosthetic leak. After this second operation moderate aortic regurgitation occurred again, in combination with severe hemolysis and recurring anemia necessitating blood transfusions. Because of progressive heart failure the patient required a third operation, but died during the operation. As Cooley stated in his letter: "Everything possible

was done to bring him through what proved to be a terminal illness. His heart disease was advanced and the risks of surgery quite substantial".

Case 14 (H.B., 43 years at operation). This patient with a known unimportant aortic stenosis underwent a vasectomy (unfortunately without antibiotic prophylaxis). One week later he became severely ill with fever and chills. He was admitted in another hospital on August 8, 1978. Temperature was 39°C, capillary pulse and Duroziez sign were positive. Aortic stenosis murmur grade 2/6 and aortic regurgitation murmur grade 3/6 were heard. Blood cultures showed staphylococcus albus. He was treated with orbenin and gentamycin intravenously. Three days after admission he suddenly became dyspneic; the murmur of aortic regurgitation became louder. Despite digitalis and diuretics signs of left heart failure increased with impairment of renal function. He was referred to the intensive care department of the St. Radboud Hospital on August 21. Upon examination he was lethargic, with severe left heart failure due to massive aortic regurgitation. He was treated immediately by PEEP (positive end expiratory pressure). Echocardiographic examination revealed a dilated, hyperkinetic left ventricle and an early closure of the mitral leaflets. The aortic valves were not thickened; the diastolic closure point was excentric, indicating a bicuspid valve. One day after admission a Scribnershunt was placed in his right leg because of renal failure and future dialysis. He was operated on August 23. A bicuspid aortic valve was found with a 1 cm perforation in the largest valve. The aortic annulus was of a bad quality with necrotic tissue at the right- and partly the non-coronary cusp side. There was a small aneurysm in the aorta just above the non-coronary cusp. Another aneurysm was found in the proximal part of the interventricular septum with a diameter of approximately 1 cm. The aneurysms were closed with mattress sutures on dacron and a Carpentier-Edwards bioprosthesis was subsequently implanted. One week after operation his blood pressure fell and a continuous murmur was heard at the left sternal border. Supravalvular aortography revealed aortic regurgitation grade 3+ with opacification of the right atrium and right ventricle. He was re-operated upon on August 31: the prosthetic valve was partly dehisced from the aortic annulus at the necrotic area, found at first operation. A connection was found between left ventricle and right atrium and between left and right ventricle at the place of the interventricular septum aneurysm, closed at first operation. The original prosthesis was excised

and a Björk-Shiley prosthesis inserted with mattress sutures on dacron. Via right atrio-ventriculotomy the opening in the septum was closed with mattress sutures on teflon felt. One week after this second operation sputum and blood cultures showed pseudomonas aeruginosa and the patient was treated with a combination of floxapen, tobramycin, penicillin and myconasol. On September 13, a tracheostomy was performed because of insufficient respiration. Ten days later a right-sided pneumothorax occurred, treated with pleural drain. On October 7, his temperature rose to 39.8°C, E.coli was cultured from the blood. The infection did not respond to high doses of antibiotics. He died October 12, 1978. Autopsy revealed a massive bronchopneumonia in both lungs and mediastinitis. The heart was dilated, all sutures of the prosthetic valve were intact.
Comment: staphylococcus albus bacteremia after vasectomy causing acute endocarditis with perforation of aortic valve, extensive necrosis of aortic annulus and aneurysm formation in the septum. A second operation was necessary because of prosthetic valve dehiscence and left to right shunt due to perforation of the septum. He died because of severe pulmonary infection.

Case 23 (T.v.H., 19 years at operation). A female heroin addict was admitted on April 4, 1980, in another hospital because of a few days history of fever, chills, headache and nausea. Examination revealed a moderately ill and poorly nourished female without evidence of heart failure. A grade 2/6 systolic ejection murmur was heard. A few conjunctival and abdominal petechiae were seen. There was a small abscess on the lateral side of the right foot. Blood culture showed staphylococcus aureus. She was treated with floxapen and kanamycin parenteral. During treatment an aortic regurgitation murmur became evident with positive capillary pulse and Duroziez sign. On the chest X-ray the heart became enlarged compared to the normal configuration on the first chest X-ray. After treatment with digitalis and diuretics signs of left heart failure disappeared. M-mode echocardiography demonstrated a dilated hyperkinetic left ventricle. During systole multiple echoes were seen on the right- and non-coronary cusp of the aortic valve without restriction of motion; during diastole multiple dense shaggy echoes were seen in the middle of the aortic root. No abnormalities were seen on right-sided cardiac valves. The two-dimensional echocardiographic study confirmed the findings. On the short-axis view 3 aortic leaflets were seen and all 3 leaflets appeared to be thickened. Because of persisting temperature

despite adequate antibiotic treatment, mild heart failure,and the findings at echocardiography suggesting vegetations, she was operated upon (May 1, 1980). A trileaflet aortic valve was found, all 3 cusps were covered with multiple polypoid appearing fresh vegetations. Part of the right coronary cusp was destroyed. A Björk-Shiley prosthesis was inserted. Cultures of the valvular tissue removed at the time of operation were sterile. Microscopic sections of the valve revealed acute inflammation and clumps of gram-positive bacteria were present. Postoperatively she was treated with floxapen and gentamycin intravenously. Oral rivadin was given during 2 weeks. The temperature was normal 2 days after operation. The total duration of antibiotic treatment was 6 weeks. After discontinuation of the antibiotics the temperature remained normal and she was discharged 6 weeks after operation. She was controlled by the drug addict team in Nijmegen and indeed did not seem to be using drugs anymore. However, on September 26, 1980, she was found dead in her bed at home. Syringe and needle were found near the patient. Her physician saw some recent needle "tracks" on her left arm and concluded that she died of heroin overdose.
Comment: in this female narcotic addict a staphylococcus aureus endocarditis occurred, causing moderate severe aortic regurgitation. The main indication for operation was persisting fever despite adequate antibiotic treatment. After replacement of her aortic valve by a prosthesis she was doing well, but died 5 months after operation probably because of a heroin overdose.

Case 25 (R.v.G., 23 years at operation). This patient with Down's syndrome (trisomy 21) was known at the pediatric department in our hospital to have chronic hepatitis (since 1970) and thrombopenia e.c.i. He was treated with 2.5 mg prednison daily. On March 29, 1981, he was admitted to our hospital because of fever and chills occurring one day before admission. Physical examination disclosed a very ill looking man with trisomy 21 symptoms. Temperature 39.4^{o}C, blood pressure 130/75 mmHg. At auscultation a grade 2/6 aortic regurgitation murmur was heard. Capillary pulse and Duroziez sign were negative. Blood cultures showed beta-hemolytic streptococcus group B. The heart was not enlarged on chest X-ray. On the echocardiogram the right coronary cusp was thickened, the left ventricle dimension was normal; a fine diastolic flutter was seen on the anterior mitral leaflet. He was treated with penicillin intravenously in combination with oral broxil

during 4 weeks. The temperature normalised after 5 days. One week after cessation of antibiotic treatment he became dyspneic. The murmur was definitely louder and the chest X-ray revealed cardiomegaly and pulmonary venous congestion. On the echocardiogram the left ventricle was dilated and hyperkinetic. There was a premature closure of the mitral valve. Two aortic valves could clearly be seen and these valves were no more thickened, one of the valves prolapsed during diastole in the left ventricular outflow tract. He was treated with salt restriction, digitalis and diuretics. Despite this treatment left-sided heart failure persisted. At cardiac catheterization the mean pulmonary artery wedge pressure was 35 mmHg, pulmonary artery pressure 70/28 mmHg, aorta pressure 100/40 mmHg. Supravalvular aortography revealed aortic regurgitation grade 4+. Surgery was performed on June 29, 1981: the right coronary cusp of the (tricuspid) aortic valve was partly detached from the aortic annulus. A Ionescu-Shiley bioprosthesis was implanted. Culture of left atrial line one week after operation was positive for streptococcus faecalis; from the urine proteus mirabilis was cultured. He received amoxicillin 375 mg 3 times daily during 10 days. Because of persisting problems with miction on the base of urethral stricture, an urethrotomy was performed by the urologist under general anesthesia and with proper antibiotic prophylaxis. He was discharged from the hospital 3 weeks after cardiac surgery with a normal bodytemperature. Three weeks after dismissal he was re-admitted because of high fever. Blood cultures and urinary culture grew streptococcus faecalis. He was treated with penicillin and gentamycin intravenously. On the echocardiogram made at admission the left ventricle dimension was normal. The bioprosthesis leaflets were thickened and the systolic separation was not optimal. Two and a half weeks after this second admission a grade 3/6 aortic regurgitation murmur was heard and the chest X-ray showed enlargement of the heart compared to the X-ray at admission. On the echocardiogram the left ventricle dimension was increased with a fine diastolic fluttering occurring on the anterior mitral leaflet. His hemodynamic situation was stable. On September 16, he complained of abdominal pain, 2 days later of severe pain in his right back and left upper abdominal regio. On September 21, progressive dyspnea developed; the chest X-ray showed pulmonary edema and the cardiac murmur was hardly heard. Because of signs of shock thought to be caused by severe aortic regurgitation, he was transported to the operation room, but died before operation could take place. At autopsy the 3 leaflets of the bio-

prosthesis were fused together at the commissure side; the leaflets were fibrotic and calcified. At 3 places the sewing ring of the prosthesis was disrupted from the aortic root. Local infarcts were found in spleen and right kidney.
Comment: this patient with Down's syndrome underwent aortic valve replacement 2 months after completion of antibiotic treatment for beta-hemolytic streptococcus endocarditis. Six weeks after this operation an "early" prosthetic valve endocarditis occurred, caused by streptococcus faecalis (Source: left atrial line or urinary tract infection). Infection resulted in paraprosthetic regurgitation and systemic emboli (splenic and renal). He died because of sudden exacerbation of the aortic regurgitation causing shock.

Case 39 (A.V., female, 65 years at operation). She underwent a Björk-Shiley mitral valve replacement because of severe (rheumatic) mitral regurgitation in April 1980. Two weeks after the operation she became febrile and blood cultures were positive for staphylococcus aureus. Woundculture at the site of the (removed) left atrial line was positive for the same micro-organism. Erythromycin was given during 2 weeks, 1 g daily. One month after the operation she was discharged with a normal temperature. Six weeks later she was admitted again to another hospital because of fever and shaking chills. Again blood cultures were positive for staphylococcus aureus. She was treated with flucloxacyllin in combination with gentamycin parenteral during 6 weeks. Her temperature normalized two days after initiation of this therapy and remained normal the whole time. She was discharged but re-admission followed two weeks later on August 25, because of fever and chills. Again staphylococcus aureus was found on blood cultures and she received the same antibiotics. After 3 days the temperature again was normal. Two weeks after admission a mitral regurgitation murmur was heard. At the same time she became dyspneic. Despite treatment with salt restriction, digitalis and diuretics she showed increasing dyspnea and was transferred to the St. Radboud Hospital. Physical examination revealed a mitral regurgitation murmur grade 3/6 at the apex with a third heart sound. Opening and closing click of the Björk-Shiley prosthesis were normal. Chest X-ray demonstrated a markedly enlarged heart with pulmonary venous distension in the upper lung fields. On the M-mode echocardiogram the left ventricle was dilated and hyperkinetic; a characteristic "hump" of the disc during the early

opening phase was seen. In addition the A2-MVO interval was short (fig.19). Cinefluoroscopy documented a marked tilting of the valve with an excursion of 30°. Swan-Ganz catheterization revealed a mean pulmonary wedge pressure of 25 mmHg with V-waves of 35 mmHg and a pulmonary artery systolic pressure of 40 mmHg. She was found to have a significant perivalvular prosthetic leak leading to severe mitral regurgitation and left heart failure. Unfortunately the temperature rose again two days before operation and blood culture showed klebsiella pneumoniae. She was treated now with cefuroxim and amikacin. Upon operation October 16, 1980, about 1/3 of the circumference of the sewing ring was found to be dislodged. The remainder of the ring showed some evidence of infection. The prosthesis was excised and a new Björk-Shiley mitral valve prosthesis was inserted. In the night after operation ventricular tachycardia occurred and persisted, despite administration of high doses of anti-arrhythmic drugs. The tachycardia was converted to sinus rhythm by electrical cardioversion. Thereafter she developed a low cardiac output syndrome with impairment of renal and cerebral functions. Ten days after operation the patient was comatose and quadriplegic. The electroencephalogram demonstrated diffuse severe changes. On November 4, she developed a bronchopneumonia and died 4 days later. Autopsy showed bronchopneumonic abscess and pyothorax on the left side. There was a transmural circular ischemia of the left myocardium. The mitral valve prosthesis was tightly inserted without signs of inflammation. Brain autopsy was not performed.

Comment: "early" prosthetic valve endocarditis 2 weeks after mitral valve replacement and caused by staphylococcus aureus. Relapses of infection 6 weeks respectively 2 weeks after termination of antibiotic therapies. The third episode of endocarditis caused partial dislodgement of the prosthesis with severe mitral regurgitation. After implantation of a new prosthesis and electrical cardioversion for ventricular tachycardia she developed a low output syndrome with cerebral deterioration. She ultimately died because of bronchopneumonic abscess and pyothorax.

3.2.13.2. Case histories of patients with troublesome (postoperative) course

Case 24 (S.T., female, 39 years at operation). On April 12, 1981, she was admitted to another hospital because of fever and chills occurring some days

after an induced ("criminal") abortion. Blood cultures showed E.coli. She was treated with a combination of keflin, gentamycin and clindamycin. Because of persisting temperature and abdominal pain she was referred to the intensive care department of our hospital on April 28. At examination she was ill, blood pressure 90/70 mmHg, pulse 110/min, temperature 39.5°C. A systolic ejection murmur grade 2/6 was heard. Abdominal palpation was very painful. Subsequently a laparotomy was performed and some yellow-green fluid was found in the right upper half of the abdominal cavity. Culture of this fluid showed staphylococcus albus. Liver, spleen, kidneys, uterus, ovariae showed no abnormalities. She continued to appear ill with persistent peaking fever. On echocardiographic examination (fig.27a and b) a large mass of echoes was seen on the right coronary cusp of the aortic valve, the systolic motion of the valve was unrestricted. On control echocardiography one week later, the vegetation appeared to be unchanged in size. Blood cultures at that time were positive for streptococcus faecalis and staphylococcus albus. She was treated now with ampicillin, keflin, amikasin. Because of signs of persisting infection with positive blood cultures and a large vegetation on the aortic valve she underwent cardiac surgery on May 19. A large, redundant, vegetation was attached on the right coronary and left coronary cusp of the aortic valve (fig.27c and d). The non-coronary cusp was normal. The valves were removed and a Björk-Shiley prosthesis was implanted. Microscopic examination of the valve revealed masses of fibrin with platelets, leukocytes, clumps of grampositive bacteria and some scattered gramnegative micro-organisms (small rods). Culture of the valve was positive for streptococcus bovis (group D hemolytic streptococ, differing from streptococcus faecalis by its sensibility to penicillin). Postoperatively the antimicrobial agents were continued during 3 weeks. Therapy was discontinued then because of hypersensitivity to the drugs (generalised rash and urticarial reaction). The patient generally improved, the temperature however failed to normalize completely, abdominal pain recurred. On abdominal echocardiographic examination a large echofree space was seen in the spleen. Because of suspicion of splenic abscess, splenectomy was performed.
After this intervention the course was uneventful and she was discharged on June 28, 1981.
Comment: this case illustrates the fact that gramnegative bacillary endocarditis is difficult to eradicate, super-infection with other micro-organisms may occur. Surgical intervention (aortic valve resection) was

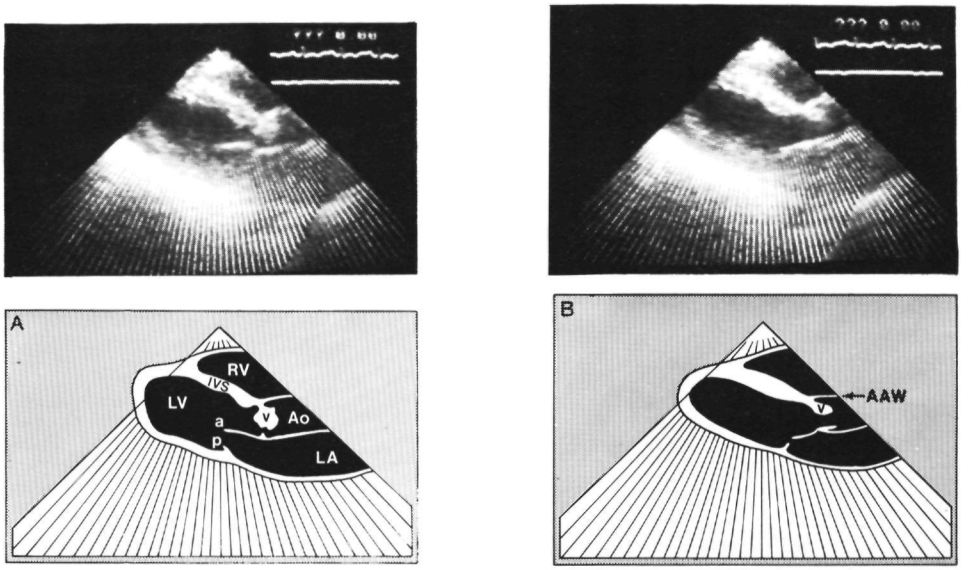
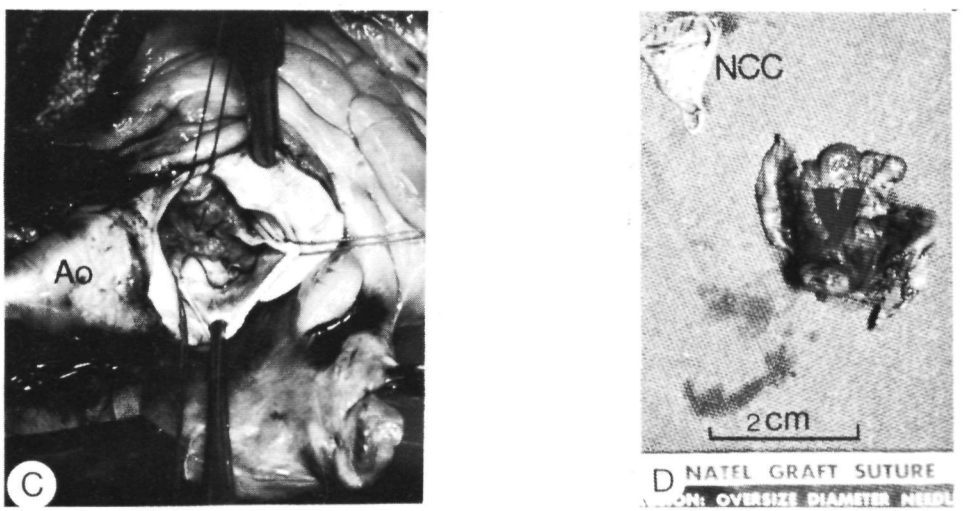


Figure 27. Two-dimensional echocardiograms accompanied by labeled, idealized diagrams. Panel A is a long-axis view, recorded during diastole: a large vegetation (V) is seen on the anterior (right coronary) cusp of the aortic valve. Panel B is a long-axis view, recorded during systole: the aortic valve leaflet with the vegetation (V) approximates the anterior aortic wall (AAW); part of the lumen of the aortic root is still occupied by the vegetation.



C. Operative photograph showing aortic orifice, nearly completely obstructed by a large vegetation (V). Ao = opened aorta.

D. Photograph of removed aortic valve leaflets, and (part of) packing of surgical tevdek suture (for measuring size of vegetation). The vegetation (V) was attached to right cusp and left cusp. Both cusps were found to be partially fused. Normal non-coronary cusp (NCC).

necessary because of persistent infection despite synergistic antibiotic drug combination. The failure of the patient's temperature to fall to normal levels after operation was the result of splenic abscess.

Case 45 (G.G., 39 years at operation). He was admitted to another hospital on January 23, 1981, with severe heart failure (pulmonary edema). The cardiologist heard an aortic regurgitation murmur. The patient was transferred to the intensive care department and treated with PEEP. He was completely dependent on PEEP respiration and after one month his condition had not improved. Blood cultures showed staphylococcus albus. He was treated with flucloxacillin and gentamycin intravenously. He was transferred to the intensive care department of our hospital on February 20. At auscultation of the heart an aortic regurgitation murmur grade 3/6 was heard, a diastolic murmur at the apex and a systolic murmur of tricuspid regurgitation. Other signs of tricuspid valve insufficiency were: pulsating neck veins and liver during systole. Echocardiographic examination showed uniformly thickened echoes in the lumen of the aortic root; a systolic valve separation could not be seen. Both mitral valve leaflets were thickened with the motion pattern of mitral stenosis. Left atrium and left ventricle were dilated with a decreased amplitude of motion of the left ventricular posterior wall and a paradoxical septal motion produced by right ventricular volume-overload due to tricuspid valve regurgitation. Two days after admission a heart catheterization was performed during PEEP-respiration. The mean pulmonary wedge pressure was 40 mmHg, artery pulmonary pressure 90/45 mmHg, left ventricle 150/20 mmHg, aortic pressure 100/60 mmHg. This patient had a severe mitral stenosis, aortic regurgitation, aortastenosis with a systolic gradient of 50 mmHg,and tricuspid valve regurgitation. He was operated upon on February 25, 1981: a bicuspid calcified aortic valve was found with a large perforation of one valve and vegetations attached to the left ventricular side of the other valve. The mitral valve was severely calcified, ostium about 1 cm^2. Both valves contained vegetations. The tricuspid valves were thickened, fibrotic and retracted. The aortic, mitral and tricuspid valves were removed and Carpentier-Edwards bioprostheses were inserted. After operation he was treated with lincomycin, rimactan, gentamycin during 4 weeks. His temperature remained subfebrile all this time, caused by sternal osteomyelitis. Soon after operation PEEP respiration was no longer necessary. Because of signs of dyspnea on slight exertion and the murmur

of aortic regurgitation a second heart catheterization took place 6 weeks after operation. The mean pulmonary wedge pressure was 20 mmHg now, pulmonary artery pressure 43/12 mmHg, left ventricle 130/15 mmHg, aortic pressure 100/70 mmHg. At ventriculography a poorly contracting dilated left ventricle was seen, no signs of mitral regurgitation. Supravalvular aortography showed aortic regurgitation grade 2. After treatment with digoxin, lasix and captopril his condition improved. After excochleation of the sternal fistula the temperature normalized. He was discharged from the hospital May 1, 1981.
Comment: staphylococcus albus endocarditis in a patient with pre-existent multiple cardiac valve pathology. Aortic valve infection caused severe aortic regurgitation rendering this patient in a very bad condition. After operation a hemodynamic unimportant aortic regurgitation is present.

Case 44 (H.O., female, 23 years at operation). A patent ductus Botalli was closed at her eighth year. At that time a soft aortic regurgitation murmur was heard. On January 8, 1981, an immature delivery took place, the child was dead. A few days later she exhibited fever and chills. Blood cultures showed staphylococcus aureus. She was treated with flucloxacillin, clindamycin and rifampicin intravenously. Temperature remained subfebrile. During treatment the diastolic murmur of aortic regurgitation became louder and the dyspnea increased despite digitalis and diuretics. Therefore she was referred to our hospital. At examination she was pale, moderately ill, splinter hemorrhages were seen on lips and subungual; the tip of one of her fingers was necrotic. Cardiac auscultation revealed an aortic regurgitation murmur grade 3/6, a loud first heart sound at the apex with a soft opening snap and a diastolic murmur grade 2/6. The electrocardiogram demonstrated sinus tachycardia 120/min, hypertrophy of left atrium. At echocardiography 3 aortic leaflets were seen with irregular thickening of their edges and a good systolic separation. The mitral valve was thickened, especially the anterior mitral leaflet with a mitral stenosis motion pattern. The mitral valve ostium was 1-1.5 cm^2. Left atrium dimension was increased; normal left ventricle dimension and wall motion.
Because of persisting temperature, systemic embolism (finger) and the findings at echocardiography suggesting vegetations on aortic valves, and moderate heart failure on the base of aortic regurgitation, she was operated upon on February 10, 1981, without prior cardiac catheterization.

At operation the aortic valve was composed of 3 thickened shortened valve leaflets; a small, fresh, vegetation was found on the edge of the right coronary cusp. There was a tight mitral stenosis with thickened calcified leaflets containing small vegetations. Aorta- and mitral valves were replaced by Ionescu-Shiley bioprosthesis valves respectively nr. 17 (surface 1.4 cm^2) and nr. 23 (surface 2.96 cm^2). After operation severe hemolysis occurred (LDH 3400 U/l, Hb 6.5 mmol/l, bilirubin 46 µmol/l) with impairment of renal function. A Scribnershunt was placed because of renal failure.
At cardiac auscultation a harsh systolic murmur grade 3/6 was heard at the base of the heart. On the echocardiogram one of the struts of the mitral valve bioprosthesis was positioned in the left ventricular outflow tract. The condition of the patient deteriorated and she was subcomatose. At cardiac catheterization on February 20, a systolic gradient of 50 mmHg was measured over the aortic valve prosthesis. The next day she was operated again: the leaflets of both prostheses had a normal aspect, a marked finding was the absence of endothelium ingrowth at the base of the sewing rings. Indeed the mitral valve appeared to be inserted in such a way that one of the struts was located in the left ventricular outflow tract. Both valves were removed and replaced by Björk-Shiley prosthetic valves nr. 21 (surface 2 cm^2) respectively 25 (surface 3.1 cm^2). After this second operation the clinical course was uneventful: temperature, LDH and renal function normalized. She was discharged from hospital on March 15, in a good condition.
Comment: staphylococcus aureus endocarditis occurring after immature delivery in a patient with pre-existent aorta- and mitral valve pathology. Persistent fever, systemic embolism (with detection of vegetations by echocardiography) and signs of left heart failure formed the indications for operation. After double valve replacement severe hemolysis occurred, cardiac catheterization revealed a systolic gradient over the aortic valve orifice. After a second operation with replacement of both bioprostheses by Björk-Shiley prostheses, the course was uneventful.

3.2.14. Comparison of pre- and postoperative electrocardiogram, chest roentgenogram and echocardiogram

A) Comparison of pre- and postoperative electrocardiograms (Table 19)
12-lead electrocardiograms performed just before operation and 7-21 days after operation could be compared in 31 of the 43 patients with left heart involvement. Pre- and postoperative Estes-scores were compared.
"Aortic group" patients (n = 19). All patients had sinus rhythm. Only in one patient (case 19) there was a first degree AV-block before and after operation. Pre-operatively 11 patients had LVH (mean Estes-score 7.4 points), four probable LVH (4 points) and

TABLE 19. Electrocardiography pre- and postoperatively in 21 patients with LVH and probable LVH prior to operation

	Pat.no.	Rhythm	Estes-score	
			pre-operative	postoperative
LVH, AG	3	SR	8	5
	6	SR	7	2
	7	SR	6	5
	9	SR	9	7
	11	SR	9	6
	12	SR	9	9
	16	SR	6	6
	17	SR	8	5
	18	SR	6	5
	19	SR	6	3
	23	SR	7	4
LVH, MG	29	SR	7	4
	38	SR	5	2
	28	AF	6	5
	34	AF	5	1
LVH, Mix	42	SR	8	7
probable LVH, AG	5	SR	4	4
	10	SR	4	1
	13	SR	4	4
	21	SR	4	1
probable LVH, MG	36	SR	4	1

four no LVH. Postoperatively the LVH disappeared in two out of 11 patients; in two patients the Estes-score remained the same; in seven patients the score decreased. In two of the four patients with probable LVH the score remained the same, it returned to normal in the other two patients.

"Mitral group" patients (n = 9). This group was composed of five patients with sinus rhythm (with normal AV-conduction time), three with atrial fibrillation and one with pacemaker rhythm. Pre-operatively five patients had LVH and probable LVH. Post-operatively the Estes-score normalized in three and decreased in two.

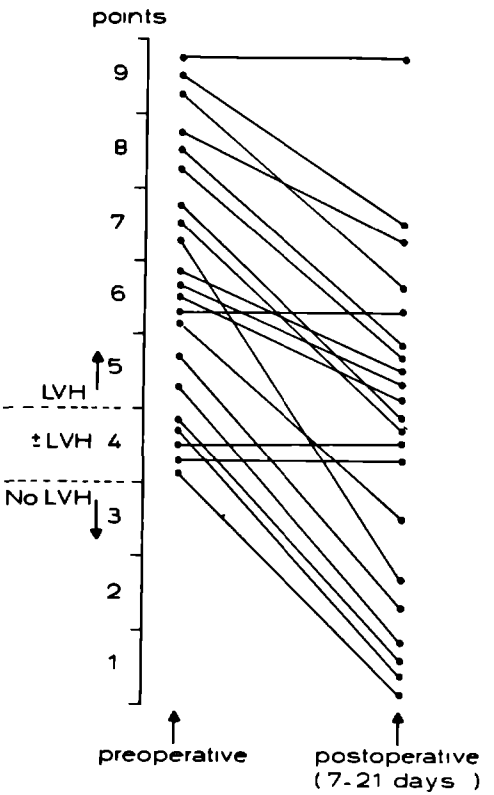


Figure 28. Pre- and postoperative Estes-score in the 21 patients with LVH and probable LVH before operation.

"Mixed group" patients (n = 3). Two of the three patients were in sinus rhythm, only one (with aortic and mitral regurgitation) had LVH pre- and postoperatively.
By combining the 3 groups there were 16 patients with LVH and five with probable LVH pre-operatively. In all of them there was a left ventricular volume overload caused by aortic regurgitation and/or mitral regurgitation. On the electrocardiogram performed 7-21 days after operation the Estes-score normalized in seven patients, LVH persisted in ten patients and probable LVH was present in four patients (figure 28).
Using the Student's t-test for paired samples, there was, even shortly after operation, a significant reduction in the post-operative Estes-score compared to pre-operative (21 paired samples; $P < 0.001$).

B) Comparison of pre- and postoperative chest roentgenograms and echocardiograms (Table 20)

Chest X-rays made shortly before operation and 7-21 days after operation could be compared in 32 of the 37 patients with pure volume overload of the left ventricle.
"Aortic group" patients (n = 20). After the operation, the heart-lung ratio (HLR) decreased in 12 patients, remained the same in four and increased in four patients. In 18 patients a pre-operative echocardiographic examination was performed; in 14 patients also postoperatively. In 13 of these 14 patients the postoperative left ventricular end-diastolic dimension (LVEDD) decreased. In only one patient did this dimension remain the same. In the four patients with an increase in the HLR on the chest X-rays postoperatively and on whom, in addition, an echocardiogram was performed, the LVEDD was diminished on the echocardiogram. In all four patients pericardial fluid was seen on the echocardiogram. In one patient (case 15) with a considerable increase in the heart-lung ratio and a large amount of pericardial fluid on the echocardiogram, a pericardial drainage had to be done because of signs of cardiac tamponade; 600 ml hemorrhagic fluid was removed. The heart-lung ratio was normal after this procedure. In the other three patients the treatment was con-

TABLE 20. Roentgenologic and echocardiographic examination pre- and postoperatively in 32 patients with left ventricular volume overload

	Case no.	PRE-OPERATIVE Chest X-ray HLR	PVV	Echocardiogram LVEDD	POSTOPERATIVE Chest X-ray HLR <	=	>	PVV	Echocardiogram LVEDD <	=	PF a	p
AG	1	0.66	+		0.63			N				
	3	0.63	+		0.58			N				
	5	0.55	+ KL	7	0.52			N				
	7	0.52	+	7.2	0.50			N	6.5		-	
	9	0.58	+	7.3	0.57			N	6		sm	
	10	0.52	N	7.1		0.52		N				
	11	0.58	++	7.5	0.50			N	7		-	
	12	0.53	+	6.5	0.47			N	5		-	
	13	0.52	+ KL	5.8	0.45			N				
	14	0.56	++	7		0.56		+		7	-	
	15	0.46	±	6.5			0.54	N	5.7		+	9 12
	16	0.56	± KL	8.5			0.63	±	8		+	5 5
	17	0.48	+	6.5		0.48		N				
	18	0.61	N	7.5	0.57			N	5.5		-	
	19	0.56	N	7.7	0.53			N	5		sm	
	20	0.52	N	7.5			0.53	N	6.2		+	0 10
	21	0.49	±	6.5	0.48			N	5.7		sm	
	22	0.53	±	7			0.60	N	6		+	10 10
	23	0.46	±	6		0.46		N	5.5		-	
	25	0.57	±	6.2	0.49			N	5		-	
MG	27	0.46	+			0.46		N				
	28	0.60	+		0.57			N				
	29	0.58	++		0 50			N				
	30	0.56	N	6	0.55			N	5.7		-	
	33	0.48	±	6	0.40			N	4.2		-	
	34	0.57	±	6.5	0.54			±	5.3		sm	
	35	0.58	+	5.5	0.55			N	4.5		-	
	36	0.68	++	6.2	0.48			N	4.7		-	
	37	0.63	++	6.0			0.65	N	4.9		+	12 10
	38	0.59	±	8.0	0.56			N	6.2		-	
Mix	41	0.63	+ KL		0.60			±				
	42	0.50	+	6.5	0.48			N	6		-	

PVV = Pulmonary venous vascularity
KL = Kerley Lines
PF = Pericardial fluid
a = echofree space anterior the heart (in mm)
p = echofree space posterior the heart (in mm)
sm = small effusion (only during systole echofree space between epi- and pericard)
N = calibre of vessels in upperlobes < lower lobes
± = " " " " " = " "
± = " " " " " > " "
++ = pulmonary edema

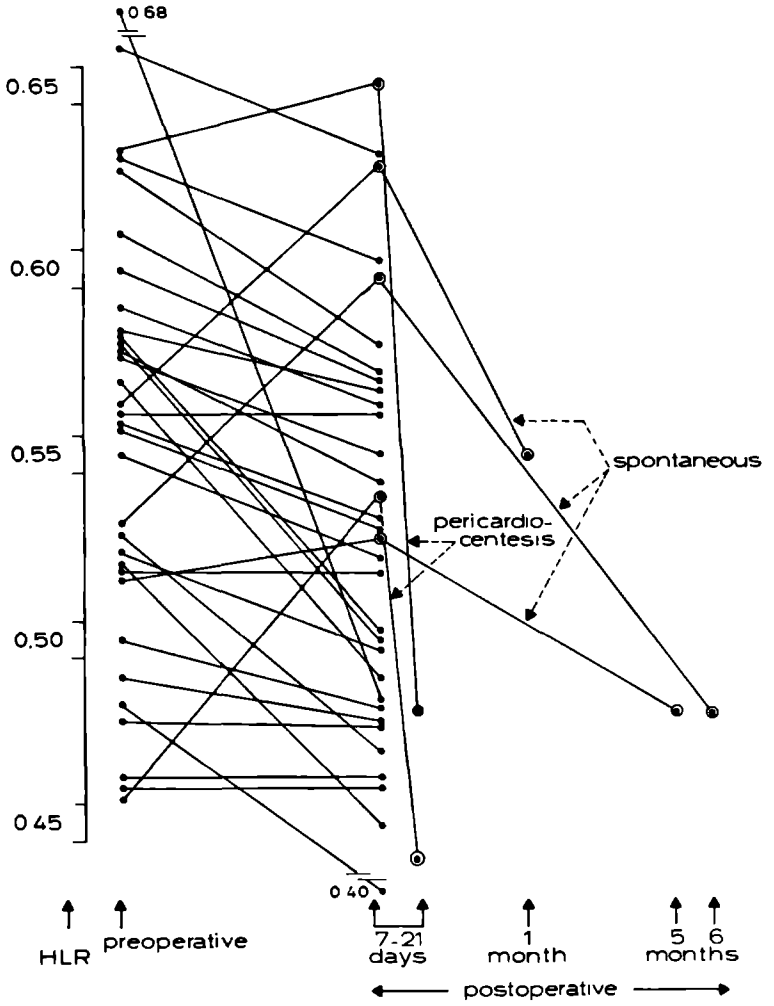


Figure 29. Pre- and postoperative heart-lung ratio (HLR) on chest X-ray in 32 patients.

servative. A control chest X-ray made respectively 6, 5 and 1 month after operation revealed a normalization of the heart-lung ratio in two patients (respectively case 20 and 22).
In case 16 the heart on the chest X-ray remained enlarged 1 month after operation. A dilated, hypocontractile left ventricle without signs of pericardial fluid was seen on the echocardiogram.
"Mitral group" patients (n = 10). After operation the HLR decreased in eight patients, remained the same in one and increased in one. In seven of the ten patients a pre- and postoperative echocardiographic examination was performed. In all seven patients the LVEDD decreased postoperatively. In the patient with increment of the HLR (case 37) a large pericardial effusion was seen on the echocardiogram. Because of signs of cardiac tamponade a pericardiocentesis was done and 460 ml hemorrhagic fluid was removed.
"Mixed group" patients (n = 2). In both patients the HLR decreased after operation.
In the combined group of 32 patients the HLR decreased in 22, remained the same in five and increased in five (figure 29). In the last five patients this increment was due to pericardial effusion, in two of them pericardiocentesis had to be done because of clinical signs of cardiac tamponade.
When the Student's t-test for paired samples was used, in order to compare the pre- and postoperative (echocardiographically determined) LVEDD, there was a significant diminution of the postoperative LVEDD (22 paired samples; $P < 0.001$).
When this test was used to compare the HLR of those patients who, in addition, underwent pre- and postoperative echocardiographic examination in which no pericardial fluid or only a small amount of pericardial fluid was seen, a significant reduction in the postoperative HLR was found (17 paired samples; $P < 0.01$).
Another important postoperative roentgenologic change was the normalization of the pulmonary vascularity. In the 27 patients with pre-operative increased calibre of upperlobe vessels or pulmonary edema, the pulmonary vascular pattern normalized 7-21 days after operation in 23 patients (85%).

TABLE 21. Clinical data of the patients in the aortic group

AORTIC GROUP

Pat. nr.	Age at oper.	Sex	Before admission: Symptoms	duration wk ≤4	duration wk >4	Findings on admission: murmur S	murmur D	spleen enlarged	ophtalmologic examination	Others
1	29	M	"Influenza"		6wk	-	-		N	SE (brain)
2	28	M	"		3M		AR			
5 (A)	51	M	" ,diplopia		2M	AS	AR		paralysis eye muscle	
6	23	M	" ,pain r.leg	3wk		-	-			mycotic an.
10	45	M	" ,cough,chills	4wk			AR		hemorrh.	
13 (A)	41	M	" ,cough,hematuria		2M		AR		N	
15	45	M	"		2M		AR	yes	N	
16	56	M	"	4wk			AR			
17 (A)	29	M	" ,nightsweat,myalgia		3M	AS		no		
18 (A)	44	M	" ,chills	4wk			AR	no		
19	32	M	Headache	3wk			AR	no	N	conjunctival petechiae
20	51	M	Influenza		7wk	AS	AR			
21	36	M	" ,nightsweat	2wk			AR		N	
22	26	M	" ,chills		3M		AR			
24 (A)	39	F	chills	2days		AS		no	N	
26	38	M	Influenza,headache	4wk		AS				
				DEATHS						
3 (A)	33	M	Janeway lesions		4M		AR	yes	some petechiae	Janeway
4	23	M	Infl.,abdominal pain		5wk	AS	AR	yes	N	clubbing,subung. hem.; SE (spleen)
7	33	M	Arthralgia,painful arm,hematuria		3M	AS	AR	no	N	mycotic an.
8 (A)	66	M	hemiparesis	2wk			AR	no	N	SE (brain)
9 (A)	27	M	Infl.,cough,arthralgia		2M		AR	yes	N	clubbing
11 (A)	23	M	chills,dyspnea	1wk		AS	AR		N	clubbing
12 (A)	54	M	Infl.,chills	3wk		AS	AR			
14 (A)	43	M	chills,nausea,vomiting	2days		AS	AR	yes		
23 (A)	19	F	chills,headache,nausea,vomiting	3days		AS		no	N	petechiae
25	23	M	chills	1day			AR		N	

(A) = patient belonging to "active group"

S = systolic
D = diastolic

N = Normal

AORTIC GROUP (1st continuation)

Pat. no.	Laboratory findings: ESR	Hb	L	globulin γ	globulin α_2	kreatinin	RA, Latex	CIC	hematuria	proteinuria	bloodculture	Pre-existent lesion	Portal of entry	Duration of AB-therapy till oper.(A)
1	92	6.8	N								str.viridans	-	?	
2											str.viridans	-	(dental caries)	
5(A)	50	6	11.6			N			-	-	str.faecalis	bic.(AcRh)	cathet.of bladder	3wk
6	67	N	12.3	18.6	N	116	-		-	-	str.viridans	-	(dental caries)	
10	21	N	16.6	22.9	10.6	N			-	-	str.viridans	-	?	
13(A)	34	N	11.0	N	N	N	+		macr.	-	str.viridans	bic.(AcRh)	?	4wk
15	35	N	N			N			-	-	str.viridans	bic.	cleaning teeth	
16											str.viridans	bic.	tooth extraction	
17(A)	24	N	N			N			-	-	str.viridans	bic.	sinus pil.oper.	6wk
18(A)											str.viridans	PV	(dental caries)	5wk
19	20	N	N	N	N	N			-	-	str.faecalis	thick valve(AcRh)	?	
20	18	N	N			N			-	-	str.viridans	dissecting aneur.	(periodontitis)	
21	48	N	N	N	N	N			-	-	str.viridans	bic.	?	
22	35	N	12			N			-	-	str.viridans	bic.	tooth extraction	
24(A)	71	5.8	N			N			20-25E	-	E.coli	-	abortion	6wk
26	92	N	11.2			N			-	-	str.viridans	bic.	tooth extraction	
									DEATHS					
3(A)	21	N	11.5	N	N	135			5-15E	+	Candida albic.	-	(dental caries)	7wk
4	19	7	N	N	N	N			-	-	str.viridans	bic.	(periodontitis)	
7	72	6.3	11.2	N	N	N			macr.	-	str.viridans	-	(dental caries)	
8(A)	41	6.2	13.4	18.6	8.9	N			2-4E	-	Diphteroid	PV	(dental caries)	5wk
9(A)	40	N	10.8	26.7	N	N			-	-	-	bic.	?	1wk
11(A)	39	6.5	11.0			115	-		-	-	-	bic.	(dental caries)	5wk
12(A)	82	5.8	N	N	N	N					str.viridans	bic.	(dental caries)	1wk
14(A)	57	6.9	N			244			-	-	staph.albus	bic.	vasectomy	1.5wk
23(A)	23	N	10.6			120			5-8E	+	staph.aureus	-	footabscess	2.5wk
25	38	N	12.9	N	N	N			-	-	ß-haemolyt.str. group B	-	(periodontitis)	

ESR = erythrocyte sedimentation rate
L = leukocytes
RA = Rheumatoid test
CIC = Circulating immunecomplex
N = Normal

E = erythrocytes/field
macr = macroscopic

(AcRh) = history of acute rheuma

(A) = patient in "active group"

AORTIC GROUP (2nd continuation)

Pat. no.	Time interval between last AB-dose and oper.(H)	Change in cardiac situation murmur	HLR	Time interval between "change" and: admission	last AB-dose	Development of HF	murmurs just before oper. S	D	Degree of HF just before oper.	Echocardiography Ratio La/Ao	ECMV	LVEDD	LVESD	FS	No.of valves	D *	V *	Others
1	1yr,9M	new	>		5wk(acute)	mod.		AR	mod.									
2	3.5M	=	=					AR	mild									
5(A)		>	>	4wk		mod.		AR	mod.	N	+	80	48	0.40	?		+	
6	2wk	new	>	5wk		mod.		AR	mild	N		72	44	0.39	?	+		widely separated AV
10	3yr	=	>		2yr	mild		AR	mild	N		71	45	0.37	3			
13(A)		=	>	2.5wk(acute)		severe		AR	severe	1.7	+	58	33	0.43	?			thick AV
15	1yr,5M	=	>		1yr(acute)	mild		AR	mild	N		76	49	0.35	2			
16	16yr	=	>		13yr	mod.		AR	mod.	1.4		95	74	0.22	2			
17(A)		>	>	2wk		mod.		AR	mod.	N	+	65	35	0.46	?	+		coarse diast. flutter AV
18(A)		=	=					AR	absent	N		75	50	0.33	PV			diast.flutter MV
19	2.5yr	=	>		2yr	mild		AR	mild	N		75	45	0.40	3			thick AV
20	10M	=	>		6wk	mod.		AR	mod.	N		77	50	0.35	3			dilated aorta
21	2.5M	=	=					AR	mild	N		75	45	0.40	?			fine diast. flutter AV
22	2wk	>	>	2wk		mod.		AR	mod.	N		70	43	0.38	2	+	+	
24(A)		=	=				EM		absent	N		50	35	0.30	3		+	
26	8.5M	new	=	1.5wk		mild	AS	AR	mild	N		67	38	0.43	2			An.IVS; thick AV
								DEATHS										
3(A)		=	=					AR	mod.									
4	5wk	>	>		2.5wk(acute)	severe		AR	severe	N	+	75	60	0.20	?		+	e.e.LVOT
7	3wk	>	>	5wk(acute)		mod.		AR	mod.	1.4		83	50	0.40	3	+	+	
8(A)		>	=	3wk				AR	absent	N		58	36	0.38	PV			diast. flutter aMV
9(A)		>	>	1wk		severe		AR	severe	N	+	73	47	0.36	?	+		widely separated AV
11(A)		=	=					AR	severe	N	+	80	60	0.25	2		+	e.e.LVOT
12(A)		new	>	1wk(acute)		severe		AR	severe	N	+	65	35	0.46	2	+	+	An.sin.Val.; e.e.LVOT
14(A)		>	=	3days(acute)		severe		AR	severe	N	+	70	32	0.54	2			
23(A)		new	>	1.5wk		mild		AR	mild	N		60	34	0.43	3		+	
25	2M	>	>		1wk	mod.		AR	mod.	1.4	+	62	33	0.47	3	+		Flail AV, e.e.LVOT

(A) = patient in "active group"
(H) = patient in "healed group"
EM = ejection murmur
* = good correlation with surgical findings
N = Normal

AORTIC GROUP (3rd continuation)

Pat. no.	Catheterization CI	AR (angio)	MR (angio)	cor.-angio	Indications for operation	Date of operation	Findings at operation No.of valves	P	D	V	Others	Examination of excised material Culture	Gram's stain	Inflammation	Type of PV
1	1.7	4+	0		HF + SE	23-8-72	3		+			ND	-	chron./fibr.	Bj-Sh
2	1.8	3+	0		HF	14-9-72	3		+			ND	+	chron.	Bj-Sh
5(A)	2.0				HF + T↑	14-10-76	2		+	+		s.faec.	ND	ND	Bj-Sh
6	4.1				HF	2-12-76	3		+	+		-	ND	ND	Bj-Sh
10	2.7	3+	0	N	HF	31-8-77	3	+				ND	+	chron.	Bj-Sh
13(A)	1.4				HF	18-7-78	2	+		+	thick AV	ND	+	chron.	Bio(CE)
15	2.0	3+	0	N	HF	18-10-78	2	+				-	-	chron.	Bio(CE)
16	2.0	3+	0	N	HF	10-11-78	2	+				-	-	chron./fibr.	Bio(CE)
17(A)	2.3	3+			HF	28-11-78	2		+	+		-	-	active	Bio(CE)
18(A)	3.0	2+			PV leak + T↑	8-2-79					PVdehisc.	-	ND	ND	Bj-Sh
19	2.8	3+	0		HF	20-3-79	3				Thick,shrunken AV	-	ND	ND	Bio(CE)
20	3.1	3+	0	N	HF	1-6-79	3				dissecting an.	ND	-	fibr.	Bio(CE)
21	3.2	3+			HF	25-1-80	2	+			prolapse 1 leaflet to LVOT	-	ND	ND	Bio(CE)
22	3.1	4+			HF	14-2-80	2		+	+		-	+	active	Bio(CE)
24(A)					T↑	19-5-81	3			+		s.Bovis	+	active	Bj-Sh
26	2.5	3+	0	N	HF	23-7-81	2			+	thick AV, large Ab	-	-	chron.	Bio(IS)
						DEATHS									
3(A)					HF + T↑	11-5-73	3	+		+	nec.ann.	ND	+	active	Bj-Sh
4	1.7				HF + SE	15-7-76	2	+		+		ND	-	chron.	Bj-Sh
7	2.8				HF	6-12-76	3		+	+	nec.ann.	-	ND	ND	Bj-Sh
8(A)					PVleak + T↑	9-5-77					nec.ann,Ab	-	ND	ND	Bj-Sh
9(A)	2.2	4+	0		HF	22-8-77	2		+	+	Ab	-	ND	ND	Bj-Sh
11(A)	1.2				HF	6-3-78	2	+		+		-	-	fibr./calc.	Bj-Sh
12(A)	1.9	4+			HF	1-4-78	2		+	+	nec.ann., An.sin.Val; thick AV	-	ND	ND	Bj-Sh
14(A)					HF + T↑	23-8-78	2	+			nec.ann.,Ab	-	+	active	Bio(CE)
23(A)	2.0	3+			HF + T↑	1-5-80	3		+	+		-	+	active	Bj-Sh
25	2.3	4+			HF	29-6-81	3		+		partly detached AV	-	-	active	Bio(IS)

T↑ = persistent fever

Calc = calcification CE = Carpentier-Edwards
fibr = fibrosis IS = Ionescu-Shiley
ND = not done Bj-Sh = Björk-Shiley

TABLE 22. Clinical data of the patients in the mitral/mixed group

Pat. no.	age at operation	Sex	Before admission: symptoms	duration wk ≤4	duration wk >4	Findings on admission: murmur S	murmur D	spleen enlarged	ophtalmologic examination	Others
MITRAL GROUP										
27	33	F				MR				
28	36	F	chills	2days		MR	MS	yes	N	
29 (A)	26	F	chills,dyspnea after delivery	0		MR		no	N	
30	38	F	cough,nausea,vomiting		3M	-	-	no		clubbing
31	45	M	infl.,acute abd.pain	2wk			MS	no	N	SE (bowel)
32	52	M	chills	3days			MS	yes		subung.hem.
33	25	F	headache,arthralgia	2wk		MR		no		
34	67	M	Janeway lesions	3wk		MR		no	N	Janeway
35	59	F	infl.		2M	MR				
36 (A)	23	M	infl.,arthralgia	4wk		MR		no		clubbing
37	36	F	myalgia,headache,lost vision	10days		-	-	no	iridocyclitis;	
38 (A)	51	F	chills	4days		MR		no	lens rupture	
			DEATH							
39 (A)	65	F	chills	5days		MR			N	
			MIXED GROUP							
40	25	F	chills after delivery	0		-	-			
41 (A)	19	F	chills,dyspnea after delivery	0		TR, MR		no	N	
42	30	M	headache,cough	1wk		AS				
43 (A)	26	F	myalgia,arthralgia,chills,cough	4wk		IPS		yes		embolus (lung)
44 (A)	23	F	chills,nausea,vom.after delivery	0			AR, MS	no	N	SE (finger), petechiae;subung. hemorrh.
45 (A)	39	M	dyspnea	2wk		AS, TI	AR, MS	no		
46 (A)	23	F	infl.,cough		5M	IPS				embolus (lung)

(A) = pat. belonging to "active group"

S = systolic
D = diastolic
N = normal

MITRAL GROUP (1st continuation)

Pat. no.	Laboratory findings ESR	HB	L	globulin γ	globulin α_2	kreatinin	RA, Latex	CIC	hema-turia	protei-nuria	blood culture	Pre-existent lesion
27											str.viridans	MV prolapse
28	25	6.9	N	19.8	N	N			-	-	str.viridans	slight MS
29(A)	60	5.5	13.6	N	9.3	N			-	-	-	ASD II
30	90	6.2	11.5	N	N	N	-		-	-	str.viridans	Myx.aMV
31	83	6.8	28.0	17.3	8.2	N	-		-	-	str.viridans	MS
32	58	N	11.6	16.5	N	N	-		5-10E	-	str.viridans	PV
33	70	N	14.4	N	N	N	-		-	-	-	thickened MV
34	130	6.0	10.7	29	N	N	-		4E	-	str.viridans	calcified AMV
35	47	N	10.2	N	N	N			-	-	str.viridans	Carpentier ring
36(A)	75	6.3	N	N	N	N	-		-	-	-	-
37	30	6.2	14.9			552	-		20E	+	staph.aureus	-
38(A)	65	5.8	13.8	22.4	N	N			-	-	staph.aureus	thickened MV(AcRh)
								DEATH				
39(A)	53	5.3	N			118			-	-	staph.aureus	PV
								MIXED GROUP				
40											staph.aureus	-
41(A)	72	6.2	14.4	25.6	8.6	N			-	-	staph.albus	-
42	100	N	12.3	N	N	N	-		-	-	-	-
43(A)	45	5.2	15.8	N	N	1060	+	+	25E	+	str.viridans	IPS
44(A)	80	6.1	17.0	N	8.4	142	-	+	5E	+	staph.aureus	MS
45(A)	60	6.9	13.3	N	N	216		+	10E	+	staph.albus	Bic.AV,MS(AcRh)
46(A)	118	6.0	16.2			N			-	-	str.viridans	IPS

ESR = erythrocyte sedimentation rate
L = leukocytes
RA = rheumatoid test
CIC = circulating immune complex
N = Normal

E = erythrocytes/field
macr = macroscopic

(AcRh) = History of acute rheuma

MITRAL GROUP (2nd continuation)

Pat. no.	Portal of entry	Duration of AB-therapy till operation (A)	Time interval between last AB-dose and operation(H)	Change in cardiac situation Time interval between "change" and: murmur	HLR	.admission	.last AB-dose	Development of HF	Murmurs just before oper. S	D	Degree of HF just before operation
27	?		11 yr	=	=				MR		mild
28	?		5 yr, 3M	=	>		4 yr	mild	MR		mild
29(A)	delivery	5.5 wk		>	>	3 wk		mod.	MR		mod.
30	(dental caries)		2 yr, 4M	new	>		1 M	mod.	MR		mod.
31	(periodontitis)		2 M	=	=					MS	absent
32	?		2 yr, 7M	=	=					"MS"	mod.
33	tooth extraction		4.5 yr	=	>		4 yr	mild	MR		mild
34	inguinal hernia op.		4 yr, 8M	=	=				MR		mild
35	cardiac operation		1 yr	=	>		5 M	mild	MR		mild
36(A)	(dental caries)	4.5 wk		>	>	3.5wk(acute)		severe	MR		severe
37	?		4.5 M	new	>		4 M	severe	MR		severe
38(A)	(periodontitis)	6 wk		=	>	3 wk		mod.	MR		mod.
					DEATH						
39(A)	cardiac operation	7 wk		>	>	2 wk		mod.	MR		mod.
					MIXED GROUP						
40	delivery		6 M	new	>	6 wk		mod.	TR		mod.
41(A)	delivery	2 wk		>	>	1 wk		severe	TR, MR		severe
42	?		2.5 M	>	=		1 M	severe	MR	AR	severe
43(A)	tooth extraction	2 wk		=	=				IPS		absent
44(A)	delivery	3 wk		>	>	2 wk		mod.		AR, MS	mod.
45(A)	?	3 wk		=	=				AS, TR	AR, MS	severe
46(A)	?	6 wk		=	=				IPS		absent

(A) = patient in "active group"
(H) = patient in "healed group"

MITRAL GROUP (3rd continuation)

Pat. no.	Echocardiography: Ratio LA/Ao	LVEDD	LVESD	FS	Rch	D	V	Others	Catheterization: CI	AR (angio)	MR (angio)	cor.-angio	Indications for operation	Date of operation
27									2.9		3+		HF	24-5-72
28									2.5		3+		HF	7-11-73
29(A)									3.3		3+		HF + T↑	27-4-76
30	1.6	60	40	0.33			"+"				3+		HF	25-6-76
31	N	50	35	0.30			+	MS	2.7		0	N	SE	23-3-77
32	N	50	30	0.40				PV normal	2.3		0		HF	14-2-79
33	1.5	60	34	0.43					2.9		3+		HF	22-3-79
34	1.4	65	38	0.42	+		+				3+	N	HF	20-4-79
35	1.4	50	30	0.40	+				1.5		3+	N	HF	21-6-79
36(A)	2.0	62	32	0.48	+		"+"	e.e.LVOT and LA	1.3				HF	16-8-79
37	1.4	52	35	0.33	+				0.8		4+	N	HF	12-9-79
38(A)	1.5	68	42	0.38				thick MV; prolapse MV	2.9				HF + T↑	12-11-79
								DEATH						
39(A)	1.6	60	38	0.37	"hump" on PV disc				1.5				HF	16-10-80
								MIXED GROUP						
40													HF (right side)	16-3-72
41(A)													HF	15-11-73
42	1.4	65	41	0.37	+	+		Flail AV; e.e. LVOT	1.4	3+	2+		HF	1-4-77
43(A)	N	45	30	0.33			+ →	AV,PuV,RVOT IPS					T↑,pulm.emb.	30-11-79
44(A)	N	47	30	0.36			+ →	AV, MS					HF + T↑ + SE	10-2-81
45(A)	2.1	56	45	0.20				Thick AV. MS	2.3	3+	0	N	HF + T↑	25-2-81
46(A)	N	50	35	0.30			+ →	PuV,RVOT,TV IPS					T↑, pulm. emb.	3-8-81

N = Normal

\+ = good correlation with surgical findings
"+" = false positive echofindings
→ = points to location of vegetations

T↑ = persistent fever

Pat. no.	Findings at operation Rch	P	D	V	Others	Examination of excised material Culture	Gram's stain	Inflammation	Type of PV
27		+			prolapse aMV	ND	-	myxomat.degener.	Bj-Sh
28		+			calc. aMV; fusion pMV	ND	-	chron.	Bj-Sh
29(A)	+			+		-	+	active	Bj-Sh
30	+				myx.aMV	-	-	active	Bj-Sh
31				+	MS	ND	-	chron.	Bj-Sh
32					PV fibr.	-	ND	ND	Bj-Sh
33		+			Short Ch.; thick MV	-	ND	ND	Bio (CE)
34	+			+	calc.aMV; scar.pMV	ND	-	calc./fibr.	Bj-Sh
35	+					-	ND	ND	Bj-Sh
36(A)	+			+	S.Ch.	-	-	active	Bio (CE)
37	+		+			ND	-	fibr.	Bio (CE)
38(A)		+		+	thick MV; prolapse pMV	-	ND	ND	Bio (CE)
					DEATH				
39(A)					nec.ann.	-	-	active	Bj-Sh
					MIXED GROUP				
40			+(TV)			ND	-	fibr.	Bj-Sh
41(A)	+(MV)		+(TV)			ND	2x-	active	2x Bj-Sh
42	+		+(AV)		Flail AV;Ab	2x-	2x-	chron.	2x Bj-Sh
43(A)				+ →	AV,PuV,RVOT. SM;IPS	3x-	ND	ND	-
44(A)				+ →	AV,MV. thick AV;MS	2x-	2x+ AV MV	active	2x Bio (IS)
45(A)		+ (AV)		+ →	AV,MV. BicAV;MS; thick TV	3x-	3x-	active AV,MV chron:TV	3x Bio(CE)
46(A)				+ →	PuV,RVOT,TV. IPS	3x-	3x+ RVOT PuV TV	active	

→ = points to location of vegetations

calc = calcification CE = Carpentier-Edwards
fibr = fibrosis IS = Ionescu-Shiley
ND = not done Bj-Sh = Björk-Shiley

Chapter 4. POSTOPERATIVE FOLLOW-UP STUDY

4.1. Aim of the study

This study was carried out in order to assess the cardiac status and to obtain a 5-year survival rate, of the patients who survived operation.

4.2. METHODS

4.2.1. Patient population

All operative survivors, with the exception of one patient who moved to America, were examined. Hence the study group was composed of 34 patients. The patients were divided into three groups, in the same way as prior to operation. The aortic group consisted of 16 patients (15 males, one female; ages 26-58 years, mean 41 years).
The mitral group consisted of 11 patients (four males, seven females; ages 25-68 years, mean 44 years).
The mixed group consisted of seven patients (two males, five females; ages 24-39 years, mean 30 years).
The patients who underwent cardiac surgery between August, 1972, and May, 1980, were examined from September 5, 1980, to December 15, 1980 (29 patients). The patients who underwent surgery in 1981 were examined in November and December 1981 (five patients). The time-interval between operation and the follow-up study ranged from 4 months to 8 years, 9 months (median 1 year, 9 months).

4.2.2. Cardiac status

The cardiac status of the patients was assessed on the basis of symptoms alone (functional cardiac status) and on the basis of findings obtained by physical, electrocardiographical, radiological, echocardiographical, and laboratory examinations.

4.2.2.1. Functional cardiac status

To categorize the functional status of the patients, the classi-

fication system formulated by the Criteria Committee of the New York Heart Association (1964) was used. In addition patients were asked whether they used a low-sodium diet or medicines.

4.2.2.2. Objective cardiac status

To categorize the objective cardiac status of the patients the classification presented by the Criteria Committee of the New York Heart Association in 1973 was used (cardiac status is graded as follows: 1. uncompromised; 2. slightly compromised; 3. moderately compromised; 4. severely compromised).
The following variables were considered.

4.2.2.2.1. Physical examination

Attention was given to height, weight, blood pressure and auscultation of the heart. Arterial blood pressures were measured with the sphygmomanometry-method (Riva-Rocci) with the patient in the recumbent position, and after echocardiography had been performed, rendering the patient in the most basal condition. Normal adult blood pressure was (arbitrarily) defined as a systolic pressure equal to or below 140 mmHg, together with a diastolic pressure equal to or below 90 mmHg. Hypertension is arbitrarily defined as a systolic pressure equal to, or greater than, 160 mmHg and/or diastolic pressure equal to, or greater than, 95 mmHg (Report of World Health Organization Expert Committee, 1978).
Auscultation of the heart was performed in the supine and sitting position. Special attention was given to intensity of heart sounds, prosthetic valve sounds and heart murmurs included. The timing, character, and location of the murmurs in relation to eventual cardiac pathology or prosthetic valve malfunction were evaluated according to the criteria of the New York Heart Association (1973). Intensity of murmurs was graded from 1 to 6 (a grade 1 murmur being very faint, a grade 6 murmur being exceptionally loud).

4.2.2.2.2. Electrocardiographic examination

Standard 12-lead electrocardiograms were recorded in all patients

at rest in supine position. Recording was done using a three channel Hewlett-Packard-electrocardiograph type 1505A.
The electrocardiograms were evaluated using the New York Heart Association criteria. Romhilt-Estes point score system was used for the assessment of left ventricular hypertrophy.

4.2.2.2.3. Roentgenologic examination

Chest X-rays were made in postero-anterior projection and left lateral projection. Heart-lung ratios were measured, i.e., the transverse diameter of the heart was divided by the greatest width of the thorax as measured from the inner margins of the ribs. A ratio of ≤ 0.50 was interpreted as normal.
Changes in cardiac size, configuration and pulmonary vascular patterns were interpreted according to the criteria of the New York Heart Association.

4.2.2.2.4. Cineradiographic examination of prosthetic valves

All patients with Björk-Shiley prosthetic valves underwent cineradiography to determine the degree of tilting of the valve ring during the cardiac cycle. Cineradiography was not done in patients with bioprosthetic valves, because the asymmetry of the metallic frame work makes measurement of degree of tilting, impossible.
Cineradiography was done in AP, LAT, LAO and RAO projection. The Björk-Shiley valve consists of a metal ring with a disc suspended between two metal struts allowing opening of the disc in one direction. The degree of rotation of the ring ("tilting") was calculated by measuring the minor and major axis of the ellipsoid projection of the ring in the minimal and maximal tilting position. The ratio of the minor (a) and major (b) axis of the ellipse can be considered as the cosine of the angle of rotation (α); $\frac{a}{b} = \cos \alpha$. The degree of rotation (R) can thus be calculated by subtracting α from α' ($R = \alpha' - \alpha$, see fig. 30).
In a study from Heystraten and Paalman (1981), tilting of Björk-Shiley aortic valves and mitral valves was evaluated in 60 patients postoperatively. When tilting was 6° or less for aortic valves, and 10° or less for mitral valves, the chance of

periprosthetic leak was small: 15% and 10%, respectively.

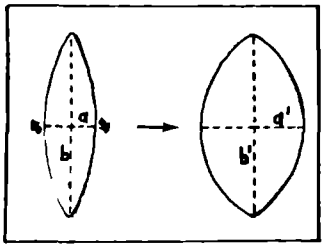


Figure 30. Method for measurement of tilting of Björk-Shiley valves.
$\frac{a}{b} = \cos \alpha$; $\frac{a'}{b'} = \cos \alpha'$
Degree of tilting = $\alpha' - \alpha$

(Reproduced by permission from Heystraten, F.M.J. and Paalman, H.: Cineradiographic evaluation of Björk-Shiley mitral and aortic valves. Ann. Radiol., 24: 346, 1981).

4.2.2.2.5. Examination of the blood

In order to assess the incidence and severity of intravascular hemolysis, the following tests were done. In addition, the method of determination and the normal values in our laboratory, are described.

Hemoglobin, hematocrit and erythrocytecount were estimated by the Hemalog method. Normal values of hemoglobin: males 8.5-11.2; females 7.5-9.9 mmol/l. Normal values hematocrit: males 0.42-0.52 l/l; females 0.37-0.47 l/l. Normal values erythrocytes: males 4.4-6.0 x 10^{12}/l; females 4.2-5.4 x 10^{12}/l. Reticulocyte count was made from films stained with brilliant cresyl blue. Normal values: males 16 $\pm$ 5°/oo; females 14 $\pm$ 5°/oo.

Serum aspartate aminotransferase (ASAT), serum alanine aminotransferase (ALAT), and serum lactate dehydrogenase (LD) were estimated according to the recommendations of the Dutch Enzyme Committee (1979). Normal values ASAT (= SGOT) $\leq$ 25 U/l; ALAT (= SGPT) $\leq$ 25 U/l; LD < 275 U/l (ASAT and ALAT were determined in order to exclude LD increment from sources other than the erythrocytes).

Serum haptoglobin was estimated by the radial immunodiffusion method of Mansini (normal values 1.8 $\pm$ 0.4 g/l) or by the nephronometry method (normal values 1000-3000 mg/l). The degree of hemolysis was classified as absent, mild or moderate.

Absent: normal haptoglobin and LD. Mild: low or absent haptoglobin, LD < 300 U/l. Moderate: low or absent haptoglobin, LD 300-400 U/l.

4.2.2.2.6. Echocardiographic examination

Two-dimensional echocardiography was performed with a commercially available wide-angle 78° phased array sector-scanner, Toshiba SSH-10A. The images were recorded on a Sanyo video cassette for subsequent analysis. Patients were examined in the slightly lateral decubitus position with the transducer in the third, fourth, or fifth left intercostal space, close to the sternal border. With the transducer in this position, the sector scan image plane was oriented parallel to the long axis of the left ventricle: "long-axis view". The transducer was then rotated 90° clockwise in order to obtain "short-axis views". Additional recordings were obtained from the apical transducer position: "apical four-chamber view". Special attention was given to the next variables:

1. Contour of the sewing ring of the Björk-Shiley valve and the stent of the bioprosthetic valve; the normal contour should be smooth and without irregularities;
2. motion of the sewing ring throughout the cardiac cycle; normal motion was considered to be the motion that would be caused by surrounding cardiac tissue to which the prosthetic sewing ring was attached;
3. thickness and integrity of porcine leaflets; normal thickness of leaflets is less than 3 mm (Schapira, 1979); the leaflets must not show erratic movement;
4. opening and closing movement of the disc in case of Björk-Shiley valves; normally the disc tilts open to an angle of 60° and returns completely in the plane through the sewing ring in closed position;
5. contraction pattern of the ventricular walls.

After these studies, M-mode echocardiography was performed as follows. By pressing the "M-mark" and "M-scan" push buttons on the operation panel, the monitor for M-mode comes into display. When a nice "long-axis" sector scan image was seen on the monitor, an M-mode "sweep" was performed by moving the slide variable resistor in such a way that the ultrasonic beam passed the aortic root with aortic valves (or prosthetic valves), the ventricular septum and left ventricular posterior wall, and the

mitral valve (or prosthetic valve) situated between them. Simultaneous lead II ECG and a carotid pulse tracing were recorded. The tracings were made with a Honeywell or Irex-strip chart recorder at a paperspeed of 25 mm/sec and 100 mm/sec. The following measurements were made from the records: Ao, LA, LA/Ao ratio, RV, LVEDD, LVESD, IVS thickness and excursion, LVPW thickness and excursion. For description and definition of these measurements, see chapter 3.1.2.
Left ventricular function was estimated by the percentage of fractional shortening (% FS) as LVEDD-LVESD/LVEDD and velocity of circumferential fibershortening (Vcf) as FS/LVET. Left ventricular ejection time (LVET) was measured as the time interval from the beginning of the upstroke of the carotid pulse wave to the onset of the dicrotic notch. This time-interval in relation to the RR-interval of the ECG was expressed as relative ejection time (RET), using the "diagram for the relative ejection time" (Hartman, 1964).
In a reference group of 20 healthy volunteers (10 males, 10 females, ages 22-49 years, mean 35 years) without evidence of heart disease, echocardiographic examination and carotid pulse tracings were performed and interpreted in an identical manner as described above in order to compare dimensions, time-intervals, and indices of left ventricular function with the three groups of our follow-up study.

4.2.3. Statistical analysis

Statistical analyses were carried out using Student's t-tests for paired and unpaired data. The level of significance was $p < 0.05$ and the data are presented as the mean $\pm$ standard deviation.
Actuarial analysis of survival was performed by the life-table method of Cutler and Ederer (1958).

4.3. RESULTS

The age and sex distribution of the patients, the time interval between operation and follow-up study, the type and position of

implantation of the prosthetic valves, and the clinical data are shown in table 23 and 24.

4.3.1. History

Twenty-two patients were feeling very well, calling themselves completely healthy: class 1, New York Heart Association.
Ten patients were in class 2, New York Heart Association: they all experienced fatigue as a result of ordinary physical activity, two patients had palpitations.
Two patients were in functional class 3, New York Heart Association: less than ordinary physical activity caused dyspnea in case 16 and fatigue in case 28.

4.3.2. Dietary measures and medication

In seven patients a dietary salt restriction of 3-5 g per day was prescribed. None of the patients had a rigid salt restriction. Twenty patients used anticoagulant drugs: 18 patients with Björk-Shiley prosthetic valves and two patients with bioprosthetic valves.
Twelve patients were on digitalis therapy, nine patients were taking diuretics (eight patients used a combination of these drugs). Two patients received a beta-blocking drug (case 41, case 43), one patient a vasodilator drug (hydralazin, case 16).

4.3.3. Physical examination

Systolic blood pressures ranged from 120 to 160 mmHg (mean 135 mmHg), diastolic pressures ranged from 70 to 105 mmHg (mean 83 mmHg). There was one patient with a borderline hypertension (case 41) and one patient with a moderate hypertension (case 43).
Upon auscultation high frequency opening and closing sounds were heard in all 18 patients with Björk-Shiley prosthetic valves. Normal heart sounds were heard in the 14 patients with bioprosthetic valves.
In all aortic group patients an ejection murmur was heard, grade 1-2/6 or 2/6. In one patient (case 6) an aortic regurgitation murmur grade 2/6 was detected.

TABLE 23. Follow-up study: clinical data of the patients in the aortic group

Pat. no.	Age(yrs) & sex	Type of PV	Time after operation yrs	month	NYHA class	Diet RS	Drugs AC	diuretic	Dig.	Physical examination Blood pressure	Murmurs timing	grade	ECG Rhythm	Estes	Chest X-ray HLR	PVP	Cineradiography
1	37 M	Bj-Sh	8	0	1	+	+		+	130/90	S	2	SR	6	0.50	N	4^{o}
2	36 M	Bj-Sh	8	0	1		+			125/85	S	2	SR	3	0.42	N	$<3^{o}$
5	54 M	Bj-Sh	4	0	1	+	+			160/90	S	2	SR	1	0.48	N	$<3^{o}$
6	26 M	Bj-Sh	3	10	1		+			135/80	S+D	2/2	SR	0	0.48	N	$<3^{o}$
10	48 M	Bj-Sh	3	1	1		+			140/90	S	2	SR	0	0.44	N	$<3^{o}$
13	44 M	Bio	2	3	2		-		+	140/90	S	2	SR	1	0.46	N	
15	47 M	Bio	2	0	1		-			150/80	S	2	SR	3	0.44	N	
16	58 M	Bio	1	10	3	+	+	+	+	140/90	S	2	SR	3	0.55	†	
17	31 M	Bio	1	10	1		-			160/90	S	2	SR	3	0.48	N	
18	46 M	Bj-Sh	1	7	2	+	+	+	+	130/75	S	2	SR	3	0.50	N	$<3^{o}$
19	34 M	Bio	1	6	2		-			120/80	S	1-2	SR	1	0.50	N	
20	52 M	Bio	1	4	2		-			120/70	S	2	SR	0	0.49	N	
21	36 M	Bio	0	8	1		-			130/90	S	1-2	SR	0	0.43	N	
22	27 M	Bio	0	7	1		-		+	150/90	S	2	SR	0	0.48	N	
24	39 F	Bj-Sh	0	5	1		+			130/80	S	2	SR	3	0.49	N	$<3^{o}$
26	37 M	Bio	0	4	1		+			130/90	S	2	SR	3	0.46	N	

RS = restriction of salt

AC = anticoagulant

TABLE 24. Follow-up study: clinical data of the patients in the mitral/mixed group

MITRAL GROUP

Pat. no.	Age(yrs) & sex	Type of PV	Time after operation yrs	mo	NYHA class	Diet RS	Drugs AC	diure-tic	Dig.	Physical examination Blood pressure	Murmurs timing	grade	ECG Rhythm	Estes	Chest X-ray HLR	PVP	Cineradio-graphy
28	43 F	Bj-Sh	7		3	+	+	+	+	130/90	S(LPS)	2	AF	1	0.60	N	12°
29	30 F	Bj-Sh	4	6	2		+			115/80	-		SR	0	0.49	N	9°
30	42 F	Bj-Sh	4	5	2		+		+	120/85	-		SR	2	0.48	N	3°
31	49 M	Bj-Sh	3	8	2		+			120/80	-		SR	0	0.46	N	3°
32	54 M	Bj-Sh	1	9	2	+	+	+	+	140/70	S(Ap)	1	AF	2	0.45	N	8°
33	27 F	Bio	1	8	1		-			130/80	S(Ap)	1-2	SR	0	0.43	N	
34	68 M	Bj-Sh	1	7	1		+	+	+	160/90	S(3L)	1-2	AF	1	0.50	N	4°
35	60 F	Bj-Sh	1	5	2		+	+	+	140/80			AF	1	0.50	N	8°
36	25 M	Bio	1	2	1		-			120/80			SR	0	0.43	N	
37	37 F	Bio	1	3	1		-	+	+	120/70	S(Ap)	1	SR	0	0.47	N	
38	52 F	Bio	1	1	1		-			150/90			SR	2	0.50	N	
								MIXED GROUP									
40	33 F	Bj-Sh(T)	8	9	1		+			120/70	-		SR	0	0.50	N	<3°
41	26 F	Bj-Sh(T,M)	7	2	1		+			140/95	-		SR	0	0.48	N	<3°
42	33 M	Bj-Sh(A,M)	3	6	1		+			120/90	S(2L)	2	SR	3	0.45	N	<3°
43	27 F	-	1	0	1	+	-	+		160/105	-		SR	0	0.42	N	
44	24 F	Bj-Sh(A,M)	0	7	1		+			130/80	S(2L)	2	SR	0	0.46	N	<3°
45	39 M	Bio(T,A,M)	0	7	2		-	+	+	140/60	S+D(3L)	2/2	AF	3	0.59	±	
46	25 F	-	0	8	1		-			120/80	D(2L)	2	SR	0	0.43	N	

A = aortic position
M = mitral position
T = tricuspid position

RS = restriction of salt
AC = anticoagulant

In the mitral group faint systolic ejection murmurs grade 1/6 or 2/6 were heard in four patients. The location of this murmur was the apical region in three patients and the third intercostal space, left parasternal in one patient.
In another patient (case 28) a blowing systolic murmur, grade 2/6, maximal near the lower sternum was heard. The murmur increased with inspiration. In addition the jugular vein pulsations showed a prominent systolic wave, and systolic pulsation of the liver was present. All these signs indicated severe tricuspid regurgitation.
In the mixed group an ejection murmur grade 2/6 was heard in both patients with combined aortic-mitral valve Björk-Shiley prostheses. In one patient with 3 bioprosthetic valves an aortic regurgitation murmur grade 2/6 was heard (case 45). In another patient who underwent resection of one of the cusps of the pulmonic valve, a pulmonic regurgitation murmur was detected (case 46).

4.3.4. Electrocardiographic examination

In the aortic group, all 16 patients had a regular sinus rhythm. Only one patient had a first degree atrioventricular block (case 18, PR interval 0.24 sec). The Estes-score was normal in 15 patients (0-3 points); only one patient met the criteria for LVH (case 1; 6 points).
In the mitral group, seven patients had a regular sinus rhythm, and four atrial fibrillation. Estes-score was normal in all (0-2 points).
In the mixed group, six patients had a regular sinus rhythm and one atrial fibrillation. The QRS-complex showed a bundle branch block pattern in three patients. A right bundle branch block in case 43 and 46 (both patients underwent a right ventriculotomy), a left bundle branch block in case 44. Estes-score was normal in all (0-3 points).

4.3.5. Roentgenologic examination

The heart-lung ratio on the chest X-rays was normal in 31 patients and increased in three patients (case 16, case 28, case

45). The pulmonary vasculary patterns were normal in 33 patients and changed in one. The change in this patient (case 16) consisted of an increased caliber of the pulmonary vessels in the upper lobes of the lung, as compared with the lower lobes.

4.3.6. Cineradiographic examination of prosthetic valves

Tilting of the ring of the Björk-Shiley aortic valves was normal ($< 6^{o}$) in all nine patients (seven in the aortic group and two in the mixed group). Tilting of the ring of the Björk-Shiley mitral valves was normal ($< 10^{o}$) in nine of the ten patients (six in the mitral group, three in the mixed group). In one patient the degree of tilting was 12^{o} (case 28, see discussion).

4.3.7. Examination of the blood (Table 25)

The hemoglobin-content of the blood was normal in 33 patients, slightly lowered in one patient (case 45). The hematocrit value was normal in 31 patients, slightly reduced in three patients (case 20, case 36, case 45).

The erythrocyte value was normal in 33 patients and slightly reduced in one (case 45).

Thus only one patient (case 45) had an anemia with reduction in number of erythrocytes and their hemoglobin-content. The mean cell volume (MCV) of this patient was increased: 100 fl (N = 85-95 fl), the mean cell hemoglobin concentration (MCHC) was normal: 20 mmol/l. These values indicate a slight macrocytic normochromic anemia.

The reticulocyte count was normal in 26 patients and elevated in eight. This increased reticulocyte content of the blood was the result of hemolysis in seven patients. The reason for this elevated count in case 43 (hemolysis absent) was unclear.

Serum ASAT and ALAT concentrations were normal in all patients.

Serum LD was normal in 23 patients and elevated in 11. Serum haptoglobin concentration was normal in seven patients and low or absent in 26. In case 16, haptoglobin was not determined (see addendum).

Hemolysis was absent in seven patients, mild in 20 and moderate in six.

TABLE 25. Examination of the blood

Pat. no.	Hb	Ht	ery's	ret.	ASAT	ALAT	LD	Haptoglobin
				AORTIC GROUP				
1	10.1	0.45	4.78	8	15	7	293	0.84 (M)
2	10.8	0.48	4.81	18	19	24	221	1.12 (M)
5	9.2	0.42	4.55	6	18	17	226	0.26 (M)
6	9.7	0.42	4.60	23	19	20	329	0.17 (M)
10	9.2	0.43	4.82	18	17	9	222	30 (N)
13	10.0	0.47	5.29	20	23	18	238	0.98 (M)
15	10.4	0.48	5.55	16	21	17	267	1.86 (M)
16	9.6	0.44	5.10	12			222	
17	9.8	0.45	4.41	17	22	20	231	360 (N)
18	9.8	0.45	5.22	20	18	7	333	±20 (N)
19	9.5	0.43	5.11	4	15	11	132	2.46 (M)
20	8.9	0.41	4.73	28	12	7	183	0.92 (M)
21	10.0	0.46	5.45	26	25	18	186	680 (N)
22	9.4	0.45	5.06	7	15	18	219	1150 (N)
24	9.7	0.46	5.54	10	16	10	239	410 (N)
26	10.1	0.44	4.65	33	20	16	318	<50 (N)
				MITRAL GROUP				
28	8.4	0.39	4.41	22	26	24	240	0 (M)
29	8.4	0.41	4.44	13	15	20	287	300 (N)
30	8.3	0.41	4.33	13	15	18	293	0.44 (M)
31	9.1	0.43	4.58	10	20	12	250	0.68 (M)
32	9.3	0.44	4.75	10	21	11	228	1360 (N)
33	8.4	0.39	4.36	16	20	18	203	2700 (N)
34	8.7	0.42	4.42	3	21	13	366	0.24 (M)
35	8.4	0.40	4.37	5	19	17	315	0.42 (M)
36	8.5	0.40	4.53	9	16	8	261	1000 (N)
37	7.7	0.38	4.30	12	19	24	269	1.00 (M)
38	8.6	0.39	4.82	17	15	13	254	0.76 (M)
				MIXED GROUP				
40	8.5	0.42	4.61	11	22	19	227	1.10 (M)
41	9.5	0.44	5.13	30	18	19	265	0.60 (M)
42	10.4	0.47	5.24	12	13	12	279	0.24 (M)
43	9.5	0.45	5.26	27	15	10	233	2320 (N)
44	9.0	0.43	4.41	18	10	19	329	0 (M)
45	8.4	0.41	4.20	36	19	17	288	0.19 (M)
46	9.4	0.44	4.65	17	15	13	238	1.2 (M)

(M) = Mansini-method

(N) = Nephronometry-method

When hemolysis was compared between aortic group patients (N = 15) and mitral/mixed group patients (N = 18), no significant difference was found in these two groups: hemolysis occurred 12 times in the aortic group and 14 times in the combined mitral/mixed group.
When hemolysis was compared between the two types of prosthetic valves, the results were as follows: hemolysis was absent in five patients with bioprosthetic valves (five of 13 = 38%) and in one patient with a Björk-Shiley valve (one of 18 = 6%).
A mild hemolysis was present in seven patients with bioprosthetic valves (seven of 13 = 54%) and in 12 with Björk-Shiley valves (12 of 18 = 67%).
A moderate hemolysis was present in one patient with a bioprosthetic valve (one of 13 = 8%) and in five with Björk-Shiley valves (five of 18 = 28%).
Absent hemolysis was more frequently encountered in patients with bioprosthetic valves, whereas moderate hemolysis was more frequently present in patients with Björk-Shiley valves. The differences, however, do not reach the level of significance.

4.3.8. Echocardiographic examination

The two-dimensional studies did not reveal abnormalities in regard to the contour of prosthetic valve sewing ring and stents; thickness and motion of bioprosthetic porcine leaflets; and opening and closing movement of the disc of Björk-Shiley valves. The abnormal structures, as seen on the pre-operative echocardiograms of the two patients with infundibular pulmonic stenosis (case 43 and case 46), were no longer present.
An abnormal contraction pattern of the ventricular wall was detected in two patients: in case 16 the left ventricle appeared to be enlarged with diffuse hypokinesis of the wall; in case 28 the right ventricle was enlarged with hyperkinesis of the wall (see discussion).
Table 26 shows the mean values (with standard deviations) of the various parameters as determined by M-mode echocardiography and carotid pulse tracings. When the variables in the three patient groups were compared with the normal group, two variables reached

TABLE 26. The mean values and standard deviations (SD) of the determined variables and parameters. Comparison between the three patient groups and the normal group

Variables	Norm.	n	AG	n	MG	n	Mix	n
Age (yrs)	35(10)	20	41 (10)	16	44 (14)	11	30 (6)	7
Echo:								
Ao (mm)	30.9(3.3)	20	37.4(5.5)	16	33.4(5.52)	11	32.6(2.1)	7
LA (mm)	32.0(4.8)	20	35.7(6.3)	16	39.4(5.4)*	11	37.6(5.6)+	7
LA/Ao(ratio)	1.04(0.15)	20	0.97(0.16)	16	1.20(0.12)o	11	1.17(0.14)	7
RV (mm)	18.0(5.2)	20	15.6(4.0)	16	21.4(6.1)	11	21.7(2.6)	7
LVEDD (mm)	47.9(3.8)	20	53.5(11.3)	16	49.2(5.2)	11	46 (4.8)	7
LVESD (mm)	30.6(3.6)	20	35.5(9.8)	16	33.5(5.0)	11	32 (5.4)	7
FS (%)	0.36(0.04)	20	0.35(0.05)	14	0.36(0.06)	9	0.33(0.03)	6
Vcf(circ./sec.)	1.19(0.12)	20	1.21(0.13)	14	1.23(0.14)	9	1.16(0.15)	6
IVS th (mm)	8.6(0.82)	20	9.0 (1.3)	16	8.7 (0.9)	11	9.4 (0.5)	7
IVS exc (mm)	5.7(1.3)	20	5.3 (2.1)	16	5.2 (2.1)	11	5.4 (2.1)	7
LVPW th (mm)	8.4(0.75)	20	9.4 (1.15)	16	8.8 (1.0)	11	9.3 (0.8)	7
LVPW exc (mm)	11.2(1.6)	20	13.3(2.3)	16	12.5(1.6)	11	9.0 (1.8)	7
Carotid pulse:								
LVET (msec)	306 (12.5)	20	292 (26.5)	16	285 (31.5)	11	282 (24.6)	7
RR (msec)	929 (94)	20	883 (112)	16	807 (65)	11	812 (101)	7
RET (%)	104 (4.2)	20	101 (8.7)	16	100 (8.9)	11	100 (7.1)	7

Norm. = Normal group
AG = Aortic group patients
MG = Mitral group patients
Mix = Mixed group patients

* = significantly different from normal group ($P < 0.001$)
o = significantly different from normal group ($P < 0.01$)
+ = significantly different from normal group ($P < 0.05$)

the level of significance. The left atrial dimension was significantly increased in the mitral group, as well as in the mixed group ($p < 0.001$ and $p < 0.05$, respectively). The left atrium/aorta was significantly increased in the mitral group only ($p < 0.01$).

4.3.9. Postoperative survival

As illustrated in figure 31, 5-year survival rates (including operative mortality) for "active group" patients and "healed group" patients are 66% and 81%, respectively. The terms "active" and "healed" are similar as used in chapter 3.1.1.: the "active group" was composed of 21 patients, operated during antibiotic therapy for IE, whereas the "healed group" was composed of 25

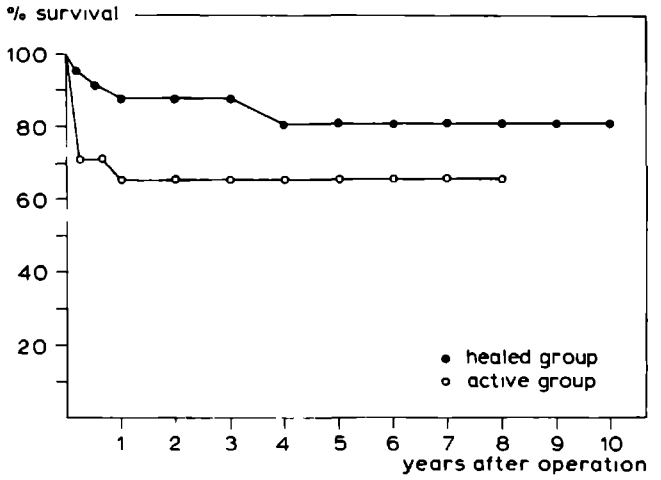


Figure 31. Actuarial cumulative survival of "active group" patients (n = 21), as compared with "healed group" patients (n = 25).

patients, operated upon after completion of antibiotic therapy. Actuarial analysis of the "active group" showed a rapid initial decline in survival during the first 3 months after operation, followed by a more gradual decline during the first year after operation. One year after operation the cumulative survival was 66% for the "active group", compared to 88% for the "healed group". Thereafter the survival remained stable in both groups. Although the "active group" had a lower survival rate over the same time period than did the "healed group", the difference was not significant. Overall 5-year survival rate (for the combined "active" and "healed" group) was 74%.

4.4. DISCUSSION AND CONCLUSION

The patients in this follow-up study were free of symptoms (22 cases) or had only few symptoms (10 cases). Two patients were severely incapacitated and these cases will be discussed separately. Upon physical examination an organic murmur of valve regurgitation was detected in four patients. A systolic murmur was heard in one patient with severe tricuspid regurgitation (case

28, see below). A diastolic murmur was heard in three patients: in two, the murmur was caused by periprosthetic aortic valve regurgitation (case 6 and case 45); in one, it was the result of pulmonic regurgitation (case 46). The regurgitant blood-volume was not large in these last three patients, since echocardiographic studies did not reveal a volume overload of the left ventricle in the first two patients, nor of the right ventricle in the last patient. Prosthetic valve function was good in 30 cases, as demonstrated by cineradiography and echocardiography. A mild periprosthetic valve regurgitation occurred in the above described two patients, indicating a slightly compromised prosthetic valve function. Echocardiographic studies on left ventricular performance, indicated a normal left ventricular function in all patients, with the exception of case 16 (see below).

The LA/Ao ratio was significantly increased in the mitral group of patients, as compared with the normal reference group.

In order to explain the discrepancy between increased LA/Ao ratio in the mitral group, as compared with the aortic group (where this parameter was normal), the corresponding parameter of the pre-operative echocardiographic examination was studied. The mean value of the pre-operative LA/Ao ratio was 1.49 (SD 1.29) in the mitral group; and was normal (1.14, SD 0.23) in the aortic group. The difference was significant ($p < 0.002$) and this was discussed in chapter 3.2.9.2. This increased LA/Ao ratio reflects a dilated left atrium. Once the left atrium is enlarged, the muscular fibers in its wall are replaced, or surrounded, by fibrous tissue (Braunwald, 1980).

After operation the LA/Ao ratio decreased significantly ($p < 0.01$, using the Student's t-test for paired samples) in the mitral group, but was still enlarged at the time of the follow-up study. The fact that the left atrial enlargement (with resultant increased LA/Ao ratio) did not regress completely after operation, might be caused by the increased amount of fibrous tissue in the wall of the left atrium.

A few remarks are to be added about two exceptional cases of this study. Case 16, male, 58 years at the time of the follow-up

study, was operated upon 1 year and 10 months earlier. A bioprosthetic valve was implanted in aortic position. Prior to operation his cardiac function was impaired with a low fractional shortening (see table 21, echocardiography). Less than ordinary physical activity resulted in dyspnea; he used a low sodium diet, diuretics, digitalis and hydralazine. The chest X-ray showed cardiomegaly with an increased caliber of the pulmonary vessels in the upper lobes. Echocardiographic examination revealed a dilated, poorly contracting left ventricle (congestive type of cardiomyopathy).

Case 28, female, 43 years at the time of the follow-up study, was operated upon 7 years earlier. A Björk-Shiley valve was inserted in the mitral position. Tricuspid regurgitation was not mentioned in the operative report, nor in pre-operative studies. Less than ordinary physical activity resulted in fatigue; she used a low sodium diet, diuretics and digitalis. Upon physical examination signs of severe tricuspid regurgitation were present. The chest X-ray showed cardiomegaly (with a normal pulmonary vasculary pattern). Upon cineradiography, the ring of the mitral valve prosthesis exhibited an exaggerated tilting motion. Echocardiographic examination revealed a dilated, hyperkinetic right ventricle. Because of these findings, she underwent a cardiac catheterization and the severe tricuspid regurgitation was confirmed. Since the increased tilting of the mitral valve ring suggested mitral regurgitation, a left ventriculogram was performed: there were no signs of mitral regurgitation.

In conclusion the functional cardiac status of the patients, according to the New York Heart Association classification, was as follows: class 1, 22 cases; class 2, 10 cases; class 3, two cases. The objective cardiac status was uncompromised in 29 cases; slightly compromised in three cases (two with mild periprosthetic leak, one with pulmonic regurgitation); and severely compromised in two cases (congestive cardiomyopathy, respectively severe tricuspid regurgitation). The 5-year survival rate of the entire patient group was 74%.

4.5. ADDENDUM

Since the data of the blood samples obtained for the study were not conclusive regarding hemolysis, letters were sent to the patients (May, 1982), requesting them to submit a second venipuncture. Only data of these second blood samples are summarized in table 25.
The actuarial postoperative survival was analyzed on July, 2, 1982, being the closing date, i.e. the survival of each patient was recorded as of that date. Case 16 had died on April, 20, 1982 (3 years and 5 months after operation). The cause of his death was congestive heart failure. Case 28, with severe tricuspid regurgitation, underwent cardiac surgery (tricuspid valve replacement by a bioprosthetic valve) on February, 6, 1982. She is doing well.

The discussion of the results of this study will take place in connection with the questions posed in the introduction.

5.1. How many adult patients underwent cardiac surgery in the St. Radboud Hospital in Nijmegen in the last 10 years during or after infective endocarditis, and what type of surgery was performed.

A total of 46 adult patients underwent cardiac surgery between 1972 and 1982 (the first patient was operated upon on May 24, 1972; the last patient on August 3, 1981). The patient population was divided into two groups.

One division was based on time of operation: when operation was performed during antibiotic treatment for IE, patients were classified into the "active group" (21 patients); when operation took place after termination of an antibiotic course, they were classified in the "healed group" (25 patients). The duration of antibiotic therapy before operation in the active group ranged from 1 week to 7 weeks, averaging 4 weeks; the time elapse between termination of antibiotic treatment and operation in the "healed group" ranged from 2 weeks to 16 years, averaging 2.4 years.

A second division was made according to the kind of operation performed: those patients who underwent aortic valve replacement because of aortic valve pathology, were categorised in the "aortic group" (26 patients); those with mitral valve replacement for mitral valve pathology formed the "mitral group" (13 patients); those patients with multiple valve involvement or right-sided IE formed a "mixed group" (seven patients).

Answer to this question (5.1).

Fourty-six adult patients underwent cardiac surgery in the last 10 years: 21 patients were operated upon during antibiotic therapy for IE; 25 patients after discontinuation of antibiotic therapy for IE. Prosthetic valve implantation was performed in 44 patients: in 26 patients in aortic position, in

13 patients in mitral position, in one patient in tricuspid position, and in four patients multiple prosthetic valves were implanted. Abnormal structures, and a valve cusp, were resected in two patients with endocarditis of the right side of the heart.

5.2. What was the clinical presentation and course of infective endocarditis.

In order to answer this question the following themes will be discussed, separately or in relation to each other: the presenting symptoms and signs; the course of the disease before diagnosis; findings on admission, such as blood cultures, murmurs, underlying heart disease, portals of entry; and the course after the disease was diagnosed.

Thirty percent of patients suffered an acute septic disease with chills and fever. They were admitted to a hospital within one week after initiation of symptoms. The causative micro-organisms for this fulminant type of infection were: five times staphylococcus aureus, twice staphylococcus albus, three times streptococcus viridans, one time Escherichia coli, unidentified in two patients with persistently negative blood cultures.

Thus the acute course of the disease was most often the result of staphylococcus aureus, a notorious virulent micro-organism, but could also be due to a "less virulent" micro-organism such as streptococcus viridans.

In the other 70% of patients the disease ran a more prolonged, semi-acute or chronic course. The duration of symptoms prior to admission ranged from 1-4 weeks in those patients with the semi-acute course and 5 weeks to 5 months in those with a chronic course. Often symptoms of low-grade fever, fatigue, malaise were ascribed to "influenza". These patients were ultimately referred to a specialist due to long duration of unexplained non-specific symptoms. Other more or less alarming presenting symptoms were: painful extremity as a result of mycotic aneurysm; abdominal pain and hemiplegia attributable to systemic embolism; skin lesions as the result of micro-emboli or vasculitis; visual disturbances due to iridocyclitis with lens rupture, respectively paralysis of an ocular muscle; and dyspnea or cough based on

left-sided heart failure or pulmonary embolism. The causative micro-organisms for this semi-acute and chronic type of infection were: streptococcus viridans, 23 times; streptococcus faecalis, twice; staphylococcus aureus and albus, one time each; candida albicans, one time, and unidentified in four patients with persistently negative blood cultures. Thus streptococcus viridans, a more indolent organism, predominated as causative agent for the more prolonged course of the disease.

With the exception of the patients with earlier inserted prosthetic material (11%), most patients (56%; 23 of 41) had no previously recognized heart disease. At operation, however, in 59% of the cases pre-existent abnormalities were encountered. In 30% no pre-existent lesions could be detected, although the extent of valvular damage often hampered judgement.

A clinically detectable portal of entry for micro-organisms was present in 39% (18 of 46) of the patients. When poor dentition (dental caries and periodontal disease) was regarded as a probable site of entrance of bacteria into the blood, this percentage was 72. A variety of procedures or conditions had been implicated in the production of IE, such as dental work, vaginal delivery, abortion, catheterization of the bladder, (extra)cardiac operations, and skin abscess. In a relatively small proportion of patients (28%; 13 of 46) with IE a portal of entry could not be identified. All but two of these 46 patients, did not receive antibiotic prophylaxis, for the most part because they were not known to have underlying heart disease.

It should be recognized, however, that even if: 1) all predisposing underlying heart disease had been recognized; 2) antibiotic prophylaxis had been given to each patient with underlying heart disease for all the above mentioned procedures; and 3) this prophylaxis had prevented all cases of IE that would otherwise have resulted from that episode of bacteremia, most cases of IE would still have occurred. The reason is that even under these optimal circumstances less than one-half of the patients (39%; 18 of 46) in our series had a recognizable portal of entry for the infecting micro-organism.

A heart murmur was detected in 89% of the patients (41 of 46)

on admission. A changing heart murmur was noted in 23 patients: in 17 during antibiotic therapy for IE, in six patients after termination of antibiotic therapy for IE. During antibiotic therapy for IE a new murmur was detected in five patients, the murmur increased in intensity in 12 patients.
After termination of antibiotic therapy for IE, a new murmur was heard in three patients, a louder murmur in another three patients. With the exception of the patient with an aortic valve prosthesis (case 8), all these patients developed some degree of heart failure. Sixty-seven percent of the patients (16 of 24) with moderate or severe heart failure prior to operation developed a gradual increase in heart failure. Thirty-three percent (eight of 24), however, experienced an attack of cardiac asthma after a period of stable cardiac function. In five patients this sudden deterioration occurred during antibiotic therapy; in three patients respectively 2.5 weeks, 5 weeks and 1 year after completion of antibiotic therapy. In retrospect, based on findings at operation, the origin of these murmurs with subsequent heart failure were: a) destruction or perforation of cardiac valves; b) rupture of chordae tendineae of the mitral valve; c) rupture of a sinus of Valsalva aneurysm into the right atrium; d) partial detachment of a Björk-Shiley valve in mitral, respectively aortic, position. The operative finding of a perforation of an aortic valve cusp in the patient with an attack of cardiac asthma one year after termination of antibiotic therapy for IE (case 15), was not conclusive in determining whether the heart failure was the result of a recent valve cusp perforation (which might have occurred despite healing) or was solely based on longstanding volume-overload of the left ventricle.

Answer to this question (5.2).
The clinical presentation had an acute character with chills and fever as presenting symptoms in 30% of patients. This fulminant type of infection was generally caused by staphylococcus aureus. In 70% of the patients the disease had a prolonged course before its diagnosis. Streptococcus viridans was the predominant causative micro-organism, responsible for this

semi-acute or chronic course. Presenting symptoms were often vague and non-specific, but could be well-defined and were sometimes alarming.
Although most patients did not have recognized heart disease prior to the occurrence of IE, in 59% of the cases pre-existent abnormalities were encountered at operation. In only 39% of the patients an apparent portal of entry for the infecting microorganisms, could be demonstrated. In 89% of patients a heart murmur was present on admission. A new or changing murmur developed later on during the illness in one-half of all patients (23 of 46), with subsequent progressive heart failure. Both new or changing murmurs and heart failure were indicative of progressively destructive events due to the infective or healing process. In the patient with an attack of cardiac asthma one year after termination of antibiotic therapy for IE, the operative findings were not conclusive in determining whether heart failure was the result of recent valve damage or was solely based on longstanding volume-overload of the left ventricle.

5.3. What were the indications for cardiac surgery.
Heart failure was the most common indication for operative intervention (87%). Thirty-nine patients had a left-sided heart failure, only one patient with severe tricuspid regurgitation developed right-sided heart failure. In eight patients operation was indicated because of critically severe, rapidly progressive heart failure. Six of them were operated upon during antibiotic treatment for IE.
Persistent infection, defined as fever despite antibiotic treatment and in the absence of a site of infection other than a cardiac structure, constituted another important indication (11%). Persistent infection occurred both in association with paraprosthetic leaks or pulmonary emboli, and as an isolated factor.
Systemic embolization necessitated valve extirpation in one patient (2%).
Echocardiography played an important role in the decision to operate two of these patients. In the patient with persistent

fever despite antibiotic treatment, a large vegetation was seen on an otherwise intact aortic valve leaflet (case 24, described sub 3.2.13.2). In the other patient (case 31) with acute abdominal pain based on an embolus to a mesenteric artery, a mild, clinically unsuspected, mitral stenosis was detected at echocardiographic examination; in addition a mass of shaggy irregular echoes, interpreted as a large vegetation, was seen on the anterior mitral leaflet some distance from the tip of this valve. On the basis of these findings the mitral valve was excised and replaced by a prosthetic valve 2 months after completion of antibiotic therapy. A lesion of approximately 1 cm in diameter was found, localized on the anterior mitral leaflet near the postero-medial commissure. At histologic examination, granulation tissue was found at the margins of the lesion; the surface of the lesion was endothelialized. These findings were consistent with a partially healed vegetation.

Answer to this question (5.3).

The indications for cardiac surgery in order of decreasing frequency were: congestive heart failure, persistent infection, and systemic embolus.

5.4. What was, in retrospect, the most reliable diagnostic aid in the assessment of cardiac anatomy as revealed by operative findings.

The fact that patients can be operated upon according to clinical findings alone is demonstrated by cases 3, 40 and 41. These patients underwent surgery in the early seventies.

A better and more sophisticated method of pre-operative investigation is provided by echocardiography and cardiac catheterization, including angiography. Both techniques can provide important information concerning valve anatomy and function, or associated cardiac pathology. In order to answer the above mentioned question both techniques are compared with the ultimate surgical findings. The results are tabulated in table 27. When the results of pre-operative echocardiography were compared with the pathologic findings at the time of surgery, the echocardiograms satisfactorily predicted 61% of the pathologic lesions. Sixty

TABLE 27. Surgical versus echocardiographic and angiographic findings

Surgical finding	Surg.n.[1)]	Echo	Surg.n.[1)]	Angio
vegetation	25	15	10	1
destruction	10	7	10	-
rupture of chordae	7	5	6	-
abscess cavity	5	1	3	3
Sinus of Valsalva-aneurysm	1	1	1	1
PV dysfunction	4	3	2	2
Total	52	32 (=61%)	32	7 (=22%)

[1)] Surg.n. = number of surgical lesions which theoretically could have been detected by pre-operative echocardiographic or angiographic examination.

percent of valves with vegetations (15 out of 25) were correctly identified pre-operatively. The other vegetations were not detected due to their: a) small size; b) location on pre-existent deformed thickened valves; and c) location on damaged, erratically moving valves. The smallest vegetation detected by echocardiography in this study had a diameter of 3 mm; the largest vegetation was 2 x 2 x 1 cm. Valve destruction was diagnosed in seven of ten cases; rupture of chordae tendineae in five of seven cases. Small abscess cavities in the upper part of the ventricular septum were not detected in four patients; a large aneurysmal cavity extending from ventricular septum into the right ventricular outflow tract was correctly identified by 2-dimensional echocardiography. A sinus of Valsalva aneurysm with rupture into the right side of the heart

was correctly diagnosed. Prosthetic valve dysfunction was diagnosed in three patients. In two patients with Björk-Shiley prostheses in aortic position the presence of paravalvular regurgitation was deduced from diastolic fluttering of the anterior mitral leaflet. The diagnosis of a significant mitral regurgitation in a patient with a Björk-Shiley prosthesis in mitral position was based on the following echocardiographic features: a) an unusual prosthetic disc "hump" in early diastole; b) a shortened A_2-MVO interval, indicating elevated left atrial pressure; and c) a dilated hyperkinetic left ventricle. In one patient with a Starr-Edwards mitral prosthesis,dysfunction was not diagnosed.

On the other hand, when results of pre-operative angiography were compared with the surgical findings, the sensitivity of angiography to detect abnormalities was low: 22%. Supravalvular aortography did not reveal aortic valve vegetations, nor did left ventricular angiography demonstrate mitral valve vegetations when these lesions were found at surgery. (In one patient with an echocardiographically documented mitral valve vegetation, this lesion was not detected on the left ventricle angiogram. Pulmonary artery angiography and subsequent filming of left atrial opacification demonstrated a small filling defect in the contrast material at the atrial side of the anterior mitral valve.)

Valve destruction and rupture of chordae tendineae as such, could not be visualized by angiography. Small abscess cavities in the proximal part of the ventricular septum were correctly identified with aortography in two patients with aortic regurgitation. In one patient with aortic regurgitation (case 26) the large "bulge" on the aortogram was thought to represent an aneurysm of the right sinus of Valsalva. Echocardiographic examination identified this "bulge" as an aneurysmal cavity, extending from the ventricular septum into the right ventricular outflow tract. In another patient with aortic regurgitation (case 12), the aneurysm of the sinus of Valsalva with rupture into the right atrium, was correctly diagnosed with a more exact localization of the site of the rupture than echocardiographic

examination had indicated. In one of the two patients with prosthetic valve dysfunction, aortography demonstrated paravalvular aortic valve regurgitation; in the other patient with a Starr-Edwards mitral valve prosthesis hemodynamic parameters demonstrated prosthetic valve stenosis.
Both techniques led to an occasional misinterpretation of abnormal findings. In two patients the surgical findings of swollen, confluent chordae tendineae of the mitral valve, and a pedunculated myxoma attached to the anterior mitral valve, respectively, were pre-operatively interpreted as vegetative lesions by the echocardiographic examiner.
The aortic "bulge" seen on the aortogram, did not represent an aneurysm of the sinus of Valsalva, but an aneurysm located just beneath the aortic valve ring in the proximal part of the ventricular septum.

Answer to this question (5.4).
Echocardiography provided the most information concerning valvular anatomy. It was less successful at revealing small myocardial, interventricular, abscess cavities as compared with angiographic examination.

5.5.1. What were the results in regard to mortality.
This question was subdivided in two questions: (1) were the results comparable with those described in the literature; and (2) which factors determined operative mortality.
5.5.1.1. What were the results in regard to mortality, were the results comparable with those described in the literature.
The overall mortality rate was 24% (11 of 46). For comparison with the results of other studies a distinction is made between early (hospital) deaths, and late deaths (6 weeks to 1 year after operation) in both "active" patients and "healed" patients. The results are summarized in table 28. The criteria for "active" and "healed" categories of patients, as used by these authors, as well as the indications for operation, were similar to those employed in our study.
In our "active group" of patients the early mortality was 29%, the late mortality 10%, and the total mortality rate was 38%

TABLE 28. Surgical mortality

	Early death (< 6 wk)				Late death (6 wk-1year)			
	Active		Healed		Active		Healed	
	%	*	%	*	%	*	%	*
Jung et al (1975)	30	(48/162)	12	(15/124)	7	(12/162)	11	(14/124)
Stinson (1979)	23	(9/39)	4	(1/27)	10	(4/39)	11	(3/27)
Jaumin et al (1981)	22	(5/23)			17	(4/23)		
This study	29	(6/21)	4	(1/25)	10	(2/21)	8	(2/25)

* (deaths/surgical patients)

(eight of 21). The early mortality rate compares closely with that described by Jung et al (30%); the percentage of late deaths is exactly the same as that of Stinson's series. The number of our "active group" patients is nearly the same as that of Jaumin et al. Although these authors reported a somewhat lower early percentage of deaths compared with our series, there were more late deaths in their series. The total mortality rate in their "active group" was 39% (nine of 23), in Jung's series 37% (60 of 162) and in Stinson's series 33% (13 of 39).
In our "healed group" of patients the early mortality was 4%, the late mortality 8%, and the total mortality rate was 12% (three of 25). The early mortality rate was lower as compared with Jung's series (12%) and similar to that published by Stinson. So, the early mortality rate in the "healed group" of patients is substantially lower than that in the "active group" of patients. An explanation for this low early mortality rate in our "healed group" of patients might be that: a) most patients

were operated upon in a relative stable state of cardiac function with moderate or only mild heart failure; and b) few technical problems were encountered by the surgeon in regard to valvular replacement; the chronic fibrosis of healed lesions, especially in the annular region, was a good environment for secure insertion of sutures.
The late mortality rate in our "healed group" of patients did not differ greatly from that of our "active group" of patients, nor from the experience of Jung et al and Stinson (11%).
The total mortality rate in our "healed group" was lower compared with that described by Jung et al (23%) and did not differ greatly from that described by Stinson (15%).

Answer to this question (5.5.1.1).
The overall mortality rate was 24%. The early, hospital, mortality rate was substantially higher in the "active group" of patients, compared with the "healed group" of patients: 38% versus 4%. Late mortality rate for the "active group" of patients did not differ greatly from that of the "healed group" of patients: 10% versus 8%. The mortality rates of our institutional experience match closely those reported by Jung et al, Stinson, and (for the "active group" of patients) Jaumin et al.
5.5.1.2. Which factors determined operative mortality.
To answer this question we searched for an eventual correlation between operative mortality and: a) infecting micro-organisms; b) the kind of operation or operative findings; c) duration of pre-operative antibiotic treatment; and d) pre-operative status of the patient. Analyses were accomplished with Vierfelder- or Student's t-test.
re a) Eventual correlation between infecting micro-organisms (as cultured from the blood) and mortality.
In three patients who died, infection with staphylococcus aureus and albus was the cause of IE (three of nine = 33%). Streptococcus viridans species were cultured in four patients in the mortality group (four of 28 = 14%). Though staphylococcal infections appear to carry a higher operative risk, the differences are not significant. The small number of patients with IE caused by candida albicans, diphteroid and those with

negative blood cultures, does not permit conclusions to be drawn.

re b) Eventual correlation between kind of operation or operative findings and mortality.

Nearly all deaths occurred in the patients with aortic valve involvement: ten deaths in the aortic group versus one in the mitral group. When mortality in the aortic group is compared with mortality in the combined mitral/mixed group the difference is significant ($p < 0.05$).

Among macroscopic pathologic findings, in six patients of the mortality group, necrotic or partly necrotic valve ring tissue was encountered: five aortic group patients, one patient in the mitral group. In three patients the friable aortic annular tissue resulted in severe paravalvular leaks. Two patients had to be re-operated for this reason, shortly after the first operation (case 12 and 14). Necrotic valve ring tissue was not encountered in any of the operative survivors.

Abscess cavities in the proximal part of the ventricular septum were found more frequently in the mortality group (27%; three of 11), compared with the operative survivor group (6%; two of 35). The difference is not significant. In two patients with these findings, however, death might have been related to these abscess cavities. In one patient with candida albicans endocarditis (case 3) an abscess was found (and debrided by the surgeon) in the proximal part of the muscular ventricular septum. In the other patient (case 9) a small cavity (erosive aneurysm) was found (and closed by the surgeon) in the atrioventricular part of the membranous septum. In both patients postoperative electrocardiographical changes occurred (left anterior hemi-block, respectively right bundle branch block in combination with left anterior hemi-block). Both patients died suddenly. A possible explanation for these sudden deaths might be a burrowing infection, respectively tissue damage or edema near the site of the closed cavity, causing interruption of the His bundle and resulting in complete heart block with asystole.

Among microscopical or bacteriological findings of excised material in eight patients of the mortality group, on whom operation was performed during antibiotic therapy, a positive

find was discovered in ten patients (77%). The difference is not significant.

re c) Eventual correlation between duration of pre-operative antibiotic treatment and mortality.

The average duration of antibiotic therapy in the eight patients in the mortality group in whom operation was performed during antibiotic therapy was 4 weeks; in the 13 operative survivors it was 4.5 weeks. The difference is not significant.

re d) Eventual correlation between pre-operative status of the patient and mortality.

In the 26 aortic group patients, five of the ten who died were operated upon during severe heart failure, whereas only one of the 16 operative survivors underwent surgery during severe heart failure ($p = 0.05$). On the other hand all five patients in the mitral/mixed group on whom surgery was performed during severe heart failure, survived. In three patients who died in hospital a pre-operative cardiac catheterization was performed (case 4, 9 and 11). Though their mean cardiac index was lower compared to the mean cardiac index of the patients in the aortic group who survived operation (1.7 versus 2.5 $l/min/m^2$) the difference was not significant ($P = 0.05$). Two of these patients were moribund (case 4 and 11) by the time operation was performed. In case 4 surgery was preceded by cardiac arrest. Death was related to delay in surgical therapy in these two patients: severe heart failure was present in both patients a few weeks before operation.

The presence of fever at the time of operation in the mortality group (36%; four of 11) did not differ significantly with pre-operative fever in the operative survivor group (20%); seven of 35). Persistent fever in combination with candida infection and delayed operative therapy was the fatal combination in case 3. He underwent surgery 1 month after diagnosis and subsequent commencement of antifungal drugs.

When the patients with an elevated serum kreatinin were regarded to have renal dysfunction, more patients in the mortality group had a compromised renal function (45%; five of 11), as compared with the operative survivor group (14%; five of 35).

The difference, however, is not significant.
An operative factor that had had an important impact on the operative outcome was neurologic damage caused by cerebral emboli prior to operation (case 8).
An interesting question is why the five patients in the aortic group, on whom surgery was performed during severe heart failure, died, while the five patients with severe heart failure in the mitral/mixed group survived. The hemodynamic status of the five patients in the aortic group was equally compromised compared with that of the patients in the mitral/mixed group: mean cardiac index 1.75 versus 1.45 l/min/m^2; and mean pulmonary wedge pressure 27 mmHg versus 31 mmHg. The average duration of pre-operative severe heart failure was virtually identical: 2.5 weeks and 3 weeks respectively. The only important differences between these 2 groups of patients were concomitant pathologic findings in all five patients in the aortic group, such as annular pathology and/or ventricular abscess cavities and/or a bad pre-operative general condition. These conditions were absent in the mitral/mixed group patients, with the exception of one patient (case 42) with a small ventricular abscess cavity.

The answer to the question (5.5.1.2) can be described as follows
The virulence of micro-organisms and the resistance to antibiotic drugs (persistent infection) affect operative mortality primarily by virtue of the severity and rapidity of valvular damage with consequent valve regurgitation and heart failure. Once heart failure is severe, operative mortality is high, especially in patients with aortic valve involvement with concomitant annular pathology and/or subvalvular myocardial abscess cavities. Important contributing risk factors for mortality are a compromised general condition, renal dysfunction and cerebral damage.

5.5.2. What were the results in regard to morbidity.
In the early postoperative period severe hemolysis occurred in a patient with Ionescu-Shiley bioprosthesis valves, requiring re-operation (case 44, described sub 3.2.13.2). Persistent fever necessitated splenectomy for a splenic abscess in one patient

(case 24, described sub 3.2.13.2) and excochleation of a sternal fistula in another patient (case 45, described sub 3.2.13.2). Cardiac tamponade occurred in two patients (case 15 and 37) and was treated with pericardial drainage. In these five patients there were no complications following the second surgical intervention.

Answer to this question (5.5.2).

There were relatively few early postoperative complications in the operative survivor group.

5.5.3. What were the results in regard to pathological/bacteriological examination of the surgically removed materal. In retrospect, was the clinical division into "active" and "healed" groups correct.

As has been described in chapter 3, re 2.11.3, 25 of the 29 specimens obtained from patients in the "active group" were cultured and only two were positive (8%). Of the 20 microscopically examined specimens, signs of activity of infection were seen 18 times (90%). This large number of microscopically positive specimens which were culture-negative suggests that histologic examination/Gram's staining is a more sensitive indicator of activity of infection or persistence of microorganisms than is culture. It may be debated whether microscopically visible organisms that do not grow in culture are viable, but for practical purposes, the presence of microorganisms in the specimens of patients, operated upon during antibiotic therapy, is regarded as a sign of active infection. If the total amount of excised material was not counted, but was checked per patient by culture and microscopic examination, then in 14 of the 21 patients signs of activity of infection were found. Hence in 67% of patients in the "active group" activity of the infective process was indeed present. Microscopic examination was not done in seven patients, because the surgeon sent the material only to the department of bacteriology. If microscopic examination had been done in all cases, then direct confirmation of active infection would have been expected in a greater proportion of cases classified as "active".

In the 25 patients of the "healed group" all cultures were negative. Five of the 25 microscopic examinations were positive (20%). In three patients with signs of activity of infection the time-interval between termination of antibiotic therapy and operation was rather short: 2 weeks, 2 months and 3.5 months. Surprisingly enough, in two patients at least one of the tests was positive a considerable time after completion of their treatment for IE. One patient was operated upon 2 years and 4 months after antibiotic treatment and histologic examination showed evidence of active inflammation. In the other patient, who underwent surgery 3 years after antibiotic therapy, gram-positive cocci were seen in the excised aortic valve. There were no signs of inflammation. Unfortunately culture of the material was not done. This last case indicates that micro-organisms may be inactively present even years after IE. The same observation was done by Christol et al (1977). They found cocci in excised material up until 1.5 years after treatment for IE. Even in the most ideal microbiological media the organisms observed in the histologic slides failed to grow. These authors concluded that the micro-organisms were definitely dead and did not present a danger for re-activation.

Answer to this question (5.5.3).
Microscopic examination of excised material appeared to be a more sensitive indicator of infection than was culture. The division in an "active" and "healed" group of patients was, in retrospect, not always accurate: in the "active group", results of microscopic examination and culture were negative in 33% of cases, whereas in the "healed group", microscopic examination showed evidence of activity of infection in 16% of cases (four of 25).

5.5.4. What were the results in regard to long-term outlook.
The results of the post-operative follow-up study, were described and discussed in chapter 4. Consideration will be given to: (1) survival; (2) cardiac status and (3) prognosis.
5.5.4.1. survival.
One year after operation the cumulative survival, calculated

by the actuarial method, was 66% for the "active group", compared to 88% for the "healed group". Five years after operation the cumulative survival remained 66% for the "active group", and was 81% for the "healed group" (one patient, case 16, died 3 years and 5 months after operation). These data compare favorably with the survival rates, as published by Stinson (1979). In his series, the 5-year survival rates for the "active" and "healed" patients were 51% and 69% respectively. Overall 5-year survival rate in our series was 74%.

5.5.4.2. cardiac status.

65% of the patients (22 of 34) were free of symptoms (class I, NYHA), 29% of the patients (10 of 34) had only few symptoms (class II, NYHA), 6% of the patients (two of 34) were severely incapacitated (class III, NYHA).

The objective cardiac status was uncompromised in 85% (29 of 34); slightly compromised in 9% (three of 34: two patients with mild periprosthetic leak, one patient with a mild pulmonic regurgitation); severely compromised in 6% (two of 34: one patient with congestive cardiomyopathy, one patient with severe tricuspid regurgitation).

5.5.4.3. prognosis.

The patient with congestive(dilated, hypocontractile) cardiomyopathy, died three years and five months after operation. The patient with severe tricuspid regurgitation underwent a tricuspid-valve replacement operation 8 years and 3 months after the first cardiac operation.

The long-term prognosis for the currently living 33 patients is similar to the prognosis for any other patient with uncompromised ventricular function and: a) prosthetic cardiac valve(s), inserted in comparable position(s), or: b) in whom surgery of the right side of the heart was performed, as in the two patients of our series with infundibular pulmonic stenosis.

Answer to this question (5.5.4).

The 5-year postoperative survival rates for "active" and "healed" patients were 66% and 81% respectively. These data compare favorably with the literature. The cardiac status was good, with two exceptions. Long-term prognosis for the currently

living patients seems favorable.

5.6. What suggestions are there for optimal treatment.
The general principles of therapy for IE are outlined in chapter 2, re 4. Detailed consideration will be given to: (1) surgical indication and timing; (2) pre-operative investigation; and (3) postoperative care.

5.6.1. What suggestions are there for optimal treatment with respect to surgical indication and timing.

By analyzing the results presented in this thesis two important points can be made. First, operative mortality for the "active group" of patients was directly related to the hemodynamic status, namely, severity of heart failure. This was the case especially in the patients with aortic valve involvement. Secondly, there was a low incidence of recurrent or persistent infection after operation (only one patient in our series). In our series of 21 patients with "active" endocarditis, surgery was based on the commonly accepted indications, such as (severe) heart failure, persistent fever, emboli. The hospital survival rate for these "active group" patients was 71% and would have been higher, in the author's opinion, had operation been undertaken before the development of severe heart failure. Since there is little correlation between operative outcome and the duration of pre-operative antibiotic treatment or intra-operative bacteriologic/histologic findings, early operation during the course of IE, irrespective of the duration of antibiotic therapy, for patients with an unfavorable prognosis, should result in improved survival. Prognosis is regarded to be unfavorable if a patient has one or more of the following seven complications and is subsequently treated with medical management alone. Therefore the following seven considerations - based on the experience of several studies[o] and our own study - are offered as guidelines

[o] Griffin et al, 1972; Mills et al, 1974; Jung et al, 1975; Parrot et al, 1976; Boyd et al, 1977; Young et al, 1978; Stinson, 1979; Jaumin et al, 1981; Rahal and Simberkoff, 1981.

indicative for cardiac surgery:

a) the development of heart failure not responding to moderate therapeutic measures, such as salt restriction, digitalis and/or low doses of diuretics, especially in association with a new or louder murmur of valve regurgitation and/or increase in heart-lung ratio on the chest X-ray. It is important to re-emphasize that the decision for operation should be based primarily on the hemodynamic deterioration. The duration of antibiotic therapy should be of secondary concern;

b) persistent infection, defined as persistent fever or persistent positive blood cultures, despite antibiotic treatment and in the absence of a site of infection other than a cardiac structure. When other causes of persistent infection, as discussed in chapter 2, re 4.2.2.2, are definitely ruled out, surgery is advised between 1 and 2 weeks after initiation of therapy;

c) systemic or pulmonary emboli when echocardiographic examination identifies (a) vegetation(s) on endocardial surface(s) of reasonable size(s). Surgery based solely on the presence of echocardiographically detected vegetations is not recommended, as vegetations may remain stable or decrease in size during or after antibiotic therapy. This was demonstrated by the study of Stewart et al (1980);

d) evidence of progressive spread of infection. A valvular focus of infection can extend to: (1) the valvular annulus (with development of an abscess or necrotic tissue); (2) the intima of the sinus of Valsalva (causing a local mycotic aneurysm); (3) the pericardial sac (causing pericarditis with pericardial effusion); and (4) the adjacent endocardium (with development of an abscess or an ulcer, which, if it does not penetrate completely, may produce a bulge. Such a bulge, often in the text of this thesis called "abscess cavity", may correctly be called an "erosive aneurysm"). An aneurysm of the sinus of Valsalva, and pericardial effusion can be demonstrated by echocardiography. Annular infection/abscess might be suspected when certain

electrocardiographic changes occur, dependent on the location of the lesion. When the infection is located in the annulus of the mitral valve at the region of the atrioventricular node, or in the annulus of the aortic valve at the region of the right fibrous trigone (through which the bundle of His passes), varying degrees of atrioventricular conduction disturbances may occur. When the infection is located in the annulus of the aortic valve at the area of the right coronary cusp and its junction with the non-coronary cusp, and extends via the membranous part of the ventricular septum (along which' inferior edge courses the bundle of His) into the proximal part of the muscular ventricular septum (where the bundle of His divides into right and left bundle branch), varying degrees of atrioventricular block and/or different bundle branch block patterns may develop.
When these electrocardiographic changes occur, permanent epicardial wires should be inserted during operation, for eventual attachment to a pacemaker unit when these abnormalities persist or progress after operation. The same strategy is advised if these electrocardiographic changes occur after debridement of necrotic annular tissue or repair of abscess cavities located in the proximal part of the ventricular septum;

e) progressively severe renal dysfunction due to circulating immune complex glomerulonephritis in the presence of verified involvement of cardiac valves or structures (this constituted an important indication for operation in case 43);

f) prosthetic valve endocarditis at the first definitive sign of prosthetic valve dehiscence. This assertion is based on the experience that loosening of a prosthesis, once initiated, is progressive and unpredictable. Infections located at the interface between prosthetic material and the tissue of the patient are relatively inaccessible for antibiotics, and are almost always accompanied by necrotic tissue or abscess formation in the valve ring or adjacent structures. Cinefluoroscopy should, in general, be performed in all patients after prosthetic valve implantation, in order that a baseline

"tilting" of the prosthetic valve ring can be determined (the method of measurement of the degree of "tilting" is described in chapter 4). When auscultatory findings or accelerating hemolysis suggest an acute change in the function of the valve prosthesis, repeat cinefluoroscopy is indicated, and, even subtle, changes in degree of "tilting" in a patient with prosthetic valve endocarditis are indicative of prosthetic valve dehiscence.

At re-operation extensive excision of infected tissue must be accomplished. Replacement with a new prosthetic valve should be carried out;

g) the established diagnosis of fungal endocarditis.

The majority of fungal endocardial infections is caused by candida species. In case of definite candida endocarditis (defined as candidemia in the presence of either a new heart murmur, arterial embolus with isolation of candida after embolectomy, or valve vegetations demonstrated by echocardiography), valve replacement should be carried out within a few days after initiation of treatment with antifungal agents. Early surgical debridement appears to be the primary form of therapy for cure, as prolonged pre-operative therapy does not aid survival. This is demonstrated by the history of case 3, described re 3.2.13.1.

In the author's opinion, surgical intervention for treatment of other particular causative organisms as proposed by Richardson et al (1978) for staphylococcal endocarditis, is not required. The mortality rate in our series of patients with staphylococcal infection was 33% and did not differ significantly from those with viridans streptococci endocarditis for example. Therapy for a patient with staphylococcal infection on native valve or prosthetic valve should be individualized and based not solely on identification of this micro-organism but on other considerations as discussed above.

These recommendations should be regarded as an attempt to relate clinical manifestations of IE to the underlying process. Generally, IE begins as a localized nidus of infection, usually

limited to leaflet tissue, in the case of heart valves, and then spreads progressively to perivalvular structures as a function of time, virulence of micro-organisms, host resistance, and effectiveness of antibiotic drugs. Once this process has fully evolved, the most favorable opportunity for operative correction in terms of removal of all infected tissue, restoration of valvular function by valve replacement, correction of any structural defects and perivalvular lesions, has already passed. Therefore when the surgical indications as described are present, there is no valid reason for delaying, and many valid reasons for proceeding with, surgery.

5.6.2. What suggestions are there for optimal treatment with respect to pre-operative investigation.

Once the decision regarding surgery is made, an accurate pre-operative characterization of localization and extension of lesions is necessary. Without this pre-operative information the cardiac surgeon may be at a serious disadvantage. The results of our study indicate that echocardiography satisfactorily predicts pathologic valve lesions and structural cardiac abnormalities. Therefore this non-invasive examination should always be performed prior to operation. Although cardiac catheterization with angiography appeared to be less sensitive in detecting valvular changes, it may demonstrate unexpected lesions, such as myocardial abscess cavities (in five patients of our study), and small intracardiac fistulas (Welton et al, 1979). Furthermore it is useful in locating the site of rupture of sinus of Valsalva (case 12). Therefore the author agrees with Welton et al (1979) that cardiac catheterization should be done, in patients with IE for whom surgery is planned, with the following comments. In patients with valve regurgitation and a stable hemodynamic state, angiography, including coronary arteriography, should be performed and is not dangerous. In patients with mitral regurgitation left ventricular angiography should be done; in patients with aortic regurgitation aortography should be done. In case of aortic regurgitation grade 3+, which means a dense opacity of the left ventricle, eventual abscess cavities or presence of mitral regurgitation may

sufficiently be demonstrated. In case of aortic regurgitation grade 2+, which means a faint opacity of the left ventricle, an eventual concomitant or suspected mitral regurgitation cannot be detected. In such a case the cardiac catheter can be positioned across the aortic valve in order to obtain a left ventricular angiogram.
Catheterization of the left side of the heart and coronary arteriography should not be performed under the following circumstances: 1) the presence of aortic valve vegetations as detected by echocardiography; 2) severe left-sided heart failure, as serious complications may occur according to a publication of Mills et al (1977). In these patients catheterization of the right side of the heart may provide safe and sufficient information about myocardial performance (cardiac index), presence of mitral regurgitation (indirectly demonstrated by increased pulmonary wedge pressure with high V-waves) or presence of intracardiac shunts (based on changes in oxygen saturation of blood samples from different compartments of the right heart, or cardiogreen-studies).
Catheterization of the right side of the heart should not be performed in patients with right-sided endocarditis in whom vegetations on valves and/or subvalvular structures are demonstrated by echocardiography. (Therefore cases 43 and 46 were operated upon only on the basis of echocardiographic examination.)

5.6.3. What suggestions are there for optimal treatment with respect to postoperative care.

The postoperative management of patients operated upon during, or shortly after, antibiotic treatment for IE is, in general, similar to that in any patient after cardiac surgery. Some detailed consideration will be given to 3 points, namely: (1) electrocardiographic changes; (2) changes in heart-lung ratio's on chest X-rays; and (3) duration of antibiotic treatment.

5.6.3.1. electrocardiographic changes.

In our series there were two patients (case 3 and 9), operated upon during antibiotic therapy, who developed bundle branch blocks postoperatively. This condition seemed to have suddenly progressed to high grade atrioventricular block with asystole.

Hence the occurrence of conduction disturbances in patients operated upon during antibiotic treatment for IE may lead to life-threatening complications. Therefore monitoring of the cardiac rhythm until approximately 2 weeks after operation is advised in those patients operated upon during antibiotic treatment for IE, with histological/bacteriological signs of active infection of the surgically removed material and/or surgically proven abscess cavities in the proximal part of the ventricular septum. In case of development of intraventricular or atrioventricular conduction disturbances, a temporary pacing wire should be inserted. At the same time a His bundle electrocardiogram should be recorded in order to evaluate the significance of atrioventricular blocks and/or bundle branch blocks. Determination of the A-H and H-V intervals can separate blocks into the more benign supraventricular lesions with A-H prolongation, or the less benign infranodal blocks with H-V prolongation or intra-His block. If the conduction disturbance persists or progresses, permanent pacing is indicated in patients with infranodal blocks.

5.6.3.2. changes in heart-lung ratio's on chest X-ray.

Comparison of chest X-rays of patients with volume overload of the left ventricle prior to operation and 7-21 days after operation, indicated that the heart-lung ratio decreased in 67% of the patients (22 of 33) postoperatively. This decrease appeared to be the result of diminution of the left ventricular end-diastolic dimension (as seen on the echocardiogram). Increment of the postoperative heart-lung ratio was always the result of pericardial fluid as demonstrated by echocardiography in five patients of our series. Pericardial drainage should be performed if there are clinical signs of cardiac tamponade.

5.6.3.3. duration of antibiotic treatment.

The duration of postoperative antibiotic therapy must be individually tailored according to its pre-operative duration. If the antibiotic course had not been completed by the time of operation (as in the "active patients"), it was then completed postoperatively. If the course had been completed pre-operatively (as in the "healed patients"), only a prophylactic antibiotic

drug effective against staphylococcus was given during the peri-operative period as described re 3.1.3.
If the results of examination of surgically removed tissue were positive (culture, microscopic examination), a more protracted course of antibiotic therapy was prescribed (4-6 weeks). Thus the duration of postoperative therapy ranged from 2 days to 6 weeks in the patients of our series.
Our study indicated that microscopic examination of surgically removed material was a more sensitive indicator of activity of infection than a culture. As the results of the examination of these specimens are important in regard to the duration of post-operative antibiotic therapy, the following suggestions can be made. After surgical removal of tissue, the particular part of the material containing pathologic lesions in which infection is apparent or suspect, should be divided by the surgeon into two samples. One sample should be sent to the department of bacteriology and one sample to the department of pathology. As micro-organisms may be situated deeply within vegetations or necrotic tissue, the material probably should be crushed or cut into multiple fragments and subsequently, cultured. This might lead to more frequent positive results concerning activity of the infectious process.

Answer to this question (5.6).

The author advocates an earlier operation when dealing with patients whose IE is associated with an unfavorable prognosis. A too rigorous conservative attitude, especially in patients with aortic regurgitation and moderate or severe heart failure often gave tragic results.
An accurate pre-operative assessment of cardiac anatomy and function is necessary in order to afford the cardiac surgeon optimal information. Echocardiography and cardiac catheterization with angiography, including coronary arteriography, should be performed with certain restrictions concerning cardiac catheterization.
In the peri- and postoperative periods strict attention must be paid to the development of conduction disturbances. Once they occur a temporary pacing wire should be inserted and a

His bundle electrocardiogram should be recorded. Permanent pacing is indicated if these disturbances persist or become worse.

An increase of the heart-lung ratio on chest X-ray may indicate pericardial fluid, sometimes necessitating pericardial drainage.

The duration of postoperative antibiotic therapy is dependent on its pre-operative duration and the results of examination of surgically removed specimens. A few suggestions are presented for a more optimal handling of these specimens.

Chapter 6. SUMMARY

The aim of this study is to review and analyze our experience in the surgical management of patients with complicated infective endocarditis (IE). To this purpose, in chapter one several initial questions are posed which will be considered in chapter 5.

Chapter 2 is a study of the literature. The first section affords information about pathogenesis and clinical features of IE. The middle section discusses diagnostic aids, and echocardiography and cardiac catheterization in particular. General principles of treatment of IE are mentioned; indications for, and aims of, cardiac surgery are discussed. In addition, some difficult surgical techniques and problems are outlined.

Chapter 3 is concerned with our own investigation. The method of composition of the patient population is described; the preoperative diagnostic aids are discussed with the emphasis on echocardiographical and angiographical criteria; the operative procedure and the method of examination of the excised material are described. A systematic enumeration is given on the clinical data prior to, during, and following operation; these data are tabulated. Characteristic illustrative material, such as echocardiograms, angiocardiograms and operative photographs, is frequently used. The case histories of the patients who died are individually described and commented upon.
The chapter finishes with two survey charts in which all relevant information up to, and including, surgery, are summarized.

Chapter 4 is a follow-up study of the patients who survived operation. This study was carried out in order to assess their cardiac status and to obtain a 5-year survival rate of the patients operated upon.

Chapter 5 is an overall discussion of the results of this study. The six questions posed in the introduction are answered in this chapter.

The first question: "how many adult patients underwent cardiac surgery in the St. Radboud Hospital in Nijmegen in the last 10 years during or after infective endocarditis and what type of surgery was performed", is answered as follows. Fourty-six adult patients underwent cardiac surgery: 21 during antibiotic therapy for IE ("active group"), 25 after discontinuation of antibiotic therapy for IE ("healed group"). Prosthetic valve implantation was performed in 44 patients; abnormal structures and a valve cusp were resected in two patients with endocarditis of the right side of the heart.

The second question: "what was the clinical presentation and course of IE", is answered as follows. The clinical presentation had an acute character with chills and fever as presenting symptoms in 30% of the patients. This fulminant type of infection was generally caused by staphylococcus aureus. In 70% of the patients the disease had a prolonged course before its diagnosis. Presenting symptoms were often vague and non-specific and were ascribed to "influenza". Streptococcus viridans was the predominant causative micro-organism. Pre-existent abnormalities were encountered at operation in 70% of the cases: earlier inserted prosthetic material was present in 11%; valvular deformities or congenital pathological lesions were found in 59% of the cases. A clinically detectable portal of entry for micro-organisms was present in only 39% of the cases. In 89% of the patients a heart murmur was heard on admission. A new or changing murmur developed later on during the illness in one-half of all the patients.

The third question: "what were the indications for cardiac surgery", is answered as follows. Congestive heart failure (89%), persistent infection (11%), and systemic embolus (2%).

The fourth question: "what was, in retrospect, the most reliable

diagnostic aid in the assessment of cardiac anatomy as revealed by operative findings", is answered as follows. Echocardiography provided most information concerning valvular anatomy and supporting structures (chordae tendineae). It was less successful at revealing small myocardial interventricular abscess cavities as compared with angiographic examination.

The fifth question (first part): "what were the results in regard to mortality", is answered as follows. Overall mortality was 24%. Hospital mortality was 38% for the "active group" patients and 4% for the "healed group" patients. Late mortality for the "active group" (10%) did not differ greatly from that of the "healed group" (8%). The mortality rates of our institutional experience closely match those reported by other authors. Important factors in determining operative mortality appeared to be: heart failure immediately prior to operation, annular pathology, subvalvular myocardial abscess cavities, and a compromised general condition.

The second part of the fifth question: "what were the results in regard to morbidity", is answered as follows. There were relatively few postoperative complications in the survivor group. Severe hemolysis occurred in one patient with Ionescu-Shiley bioprosthesis valves, requiring re-operation. Persistent fever necessitated splenectomy in one patient and excochleation of a sternal fistula in another patient. Cardiac tamponade occurred in two patients treated with pericardial drainage. The third part of the fifth question: "what were the results in regard to pathological-bacteriological examination of the surgically removed material. In retrospect, was the clinical division into "active" and "healed" groups, correct", is answered as follows. Microscopic examination of excised material appeared to be a more sensitive indicator of infection than a culture of the material. The division into two categories, "active" and "healed" group of patients, was, in retrospect, not always correct: in the "active group" results of microscopic examination and culture were negative in 33% of cases, in

the "healed group", microscopic examination showed evidence of infection in 16% of cases.
The fourth part of the fifth question: "what were the results in regard to long-term outlook", is answered as follows. The 5-year postoperative survival rates for "active" and "healed" patients were 66% and 81%, respectively. The cardiac status was good, with two exceptions: one patient had congestive cardiomyopathy, one patient had severe tricuspid regurgitation. Long-term prognosis for the currently living patients seems favorable.

The sixth question: "what suggestions are there for optimal treatment with respect to surgical indication and timing", is answered as follows. Cardiac surgery is indicated if one or more of the following complications occur:

1) the development of heart failure not responding to moderate therapeutic measures;
2) persistent infection;
3) systemic or pulmonary emboli when echocardiography identifies vegetation(s);
4) evidence of progressive spread of infection;
5) progressively severe renal dysfunction due to circulating immune complexes and in the presence of verified involvement of cardiac valves or structures;
6) prosthetic valve endocarditis at the first definite sign of prosthetic valve dehiscence;
7) fungal endocarditis.

An accurate pre-operative characterization of localization and extension of lesions is necessary to provide the cardiac surgeon with optimal information. Therefore, echocardiography and cardiac catheterization with angiography should be performed with certain restrictions concerning cardiac catheterization. In the peri- and postoperative periods, strict attention must be paid to the development of conduction disturbances. Once they occur, a temporary pacing wire should be inserted. At the same time a His bundle electrocardiogram should be recorded in order to evaluate the significance of atrioventricular block and/or bundle branch blocks. If, during the clinical course the con-

duction disturbance persists or progresses, permanent pacing is indicated in patients with infranodal blocks.
If the heart-lung ratio on the chest X-ray does not decrease after operation (in patients with volume overload of the left ventricle prior to operation), this may be an indication of pericardial fluid, and echocardiography should be performed. Pericardial drainage must be done in case of echocardiographically demonstrated pericardial fluid and clinical signs of cardiac tamponade. The duration of postoperative antibiotic therapy is dependent upon its pre-operative duration and the results of examination of surgically removed specimens.
If the results of these examinations are positive, a more protracted course of antibiotic therapy should be prescribed.
A few suggestions are presented for an optimal handling of these specimens.

Het doel van deze studie is om de Nijmeegse ervaring te analyseren met een groep van patienten die een hartoperatie hebben ondergaan i.v.m. infectieuze endocarditis (IE).
Hiertoe worden in het 1e hoofdstuk een zestal initiële vragen gesteld die in het laatste hoofdstuk opnieuw beschouwd zullen worden.

Het 2e hoofdstuk geeft een overzicht van
a) de symptomen en het verloop van IE met inbegrip van verdere cardiale en niet cardiale complicaties;
b) de diagnostische middelen, speciaal de echocardiografie en de hartcatheterisatie;
c) de behandeling van IE en vooral de indicaties voor cardiochirurgie, met aparte aandacht voor enkele technische problemen van chirurgische aard.

Het 3e hoofdstuk bevat de eigenlijke analyse van de Nijmeegse ervaring. Na een beschrijving van de patientenpopulatie wordt achtereenvolgens ingegaan op
a) de pre-operatieve diagnostiek, vooral de echocardiografische en angiocardiografische criteria;
b) de operatieprocedure;
c) het onderzoek van per-operatief verwijderd materiaal.
De beschrijving van de gebruikte methodes wordt gevolgd door een systematische opsomming van de patientengegevens van respectievelijk voor, tijdens en na de operatie. De gegevens van elke fase zijn samengevat in tabellen. Karakteristieke echocardiogrammen, angiogrammen en operatiefoto's zijn toegevoegd.
Tenslotte zijn de ziektegeschiedenissen van de overleden patienten beschreven en van een apart commentaar voorzien.
Het hoofdstuk eindigt met twee overzichtstabellen (nr. 21 en 22) die de relevante gegevens bevatten van vóór en tijdens de operatie.

Hoofdstuk 4 bevat een vervolgonderzoek naar de cardiale situatie

van de patienten. Door dit onderzoek werd tevens een inzicht verkregen in de 5-jaars overlevingsduur.

Het 5e hoofdstuk bespreekt de resultaten van het onderzoek aan de hand van de zes vragen gesteld in het eerste hoofdstuk.
De eerste vraag was: "Hoeveel volwassen patienten ondergingen de afgelopen tien jaar een hartoperatie tijdens of na IE en welke soort operatie werd verricht". Vastgesteld werd dat er 46 patienten geopereerd zijn, 21 tijdens de behandeling met antibiotica (aangeduid als de "actieve groep") en 25 na behandeling met antibiotica (aangeduid als de "genezen groep"). Bij 44 patienten werd een kunstklep geimplanteerd. Bij 2 patienten met rechtszijdige IE werden abnormale intracardiale structuren en een klepslip gereseceerd.
De 2e vraag was: "Hoe was de klinische presentatie en het beloop van IE". Vastgesteld werd dat bij 30% van de patienten het ziektebeeld acuut was, een fulminante infectie met koorts en koude rillingen, meestal veroorzaakt door staphylococcus aureus. Bij 70% van de patienten had de ziekte een geprotaheerd, chronisch, beloop vóór de diagnose werd gesteld. Meestal waren de symptomen vaag, atypisch, en werden geduid als "griep". Streptococcus viridans was de meest voorkomende verwekker. Pre-existente cardiale pathologie bleek bij operatie aanwezig te zijn in 70% der gevallen. Bij 11% van deze gevallen was in het verleden een cardiale prothese geimplanteerd en bij 59% waren de hartkleppen gedeformeerd of bestond congenitale pathologie. Een porte d'entree voor de infectie werd slechts in 39% van de gevallen gevonden. Bij 89% van de patienten werd een hartgeruis geconstateerd tijdens opname. Bij 50% van alle patienten werd tijdens het ziektebeloop een nieuw geruis gehoord, ofwel veranderde het geruis van karakter.
De 3e vraag was: "Wat waren de indicaties voor cardiochirurgie". Decompensatio cordis was de meest voorkomende indicatie (87%), gevolgd door persisterende infectie (11%) en arteriële embolie (2%).
De 4e vraag was: "Welk diagnostisch hulpmiddel was het meest nauwkeurig in het aantonen van de cardiale anatomie (pathologie),

zoals gevonden bij operatie". Echocardiografie verschafte de meeste informatie omtrent hartkleppen en ondersteunende structuren, zoals chordae tendineae. Kleine abcesholtes werden beter gedetecteerd met behulp van angiografie.
De 5e vraag (eerste deel) was: "Hoe waren de resultaten wat betreft mortaliteit". Het bleek dat de totale mortaliteit 24% was. De ziekenhuismortaliteit was 38% voor de "actieve groep" en 4% voor de "genezen groep". De late mortaliteit van beide groepen verschilde niet veel en bedroeg respectievelijk 10% en 8%.
Deze percentages wijken nauwelijks af van andere, vergelijkbare, studies. Factoren die een belangrijke invloed hadden op de operatiemortaliteit waren: decompensatio cordis ten tijde van de operatie, pathologie van de klepring, abcesholte(s) in het myocard en een slechte algemene conditie.
Het tweede deel van de 5e vraag was: "Hoe waren de resultaten wat betreft morbiditeit". Binnen de groep patienten waarvoor alleen morbiditeit relevant was, kwamen bovengenoemde ongunstige factoren duidelijk minder, en zeker niet in combinatie, voor. Er deden zich hier betrekkelijk weinig postoperatieve complicaties voor. Bij één patient met bioprotheses was re-operatie noodzakelijk vanwege ernstige hemolyse; bij 2 patienten met persisterende koorts werd miltextirpatie, respectievelijk excochleatie van een sternumfistel, verricht. Twee andere patienten ondergingen pericarddrainage wegens harttamponade.
Het derde deel van de 5e vraag was: "Hoe waren de resultaten van het pathologisch/bacteriologisch onderzoek van chirurgisch verwijderd materiaal. Was, achteraf, het klinisch onderscheid in "actieve" en "genezen" groep, juist". Er bleek dat microscopisch onderzoek de meest gevoelige methode was om de infectie aan te tonen. Het onderscheid in een "actieve" en "genezen" groep bleek niet altijd juist te zijn. Bij de "actieve groep" waren resultaten van microscopisch onderzoek en kweek in 33% der gevallen negatief, terwijl bij de "genezen groep" tekenen van activiteit van de infectie werden gevonden in 16% der gevallen.
Het vierde deel van de 5e vraag was: "Hoe zijn de resultaten op langere termijn". De 5-jaars overleving voor de "actieve" en

"genezen" patienten was respectievelijk 66%, en 81%. De cardiale situatie was goed, met uitzondering van 2 patienten: één patient met congestieve cardiomyopathie en één patient met ernstige tricuspidalis insufficientie. De prognose voor de thans levende patienten lijkt gunstig te zijn.

De 6e vraag was: "Welke aanbevelingen kunnen worden gedaan voor het moment van cardiochirurgisch ingrijpen, voor pre-operatief onderzoek en voor postoperatief beleid". Bij het optreden van één of meer van de hierna volgende complicaties dient cardiochirurgie op korte termijn te worden verricht:

1) decompensatio cordis, niet reagerend op betrekkelijk eenvoudige medicamenteuze therapie;
2) persisterende infectie;
3) arteriële- of longembolie, indien bij echocardiografie een vegetatie of vegetaties wordt gedetecteerd;
4) bij tekenen van uitbreiding van een intracardiale infectie;
5) bij verslechtering van de nierfunctie op basis van circulerende immuuncomplexen en bij geverifieerde cardiale pathologie;
6) endocarditis gelocaliseerd op een kunstklep, zodra zich tekenen voordoen van dehiscentie van de kunstklep;
7) fungus endocarditis.

Ter informatie van de cardiochirurg dient een nauwgezet preoperatief onderzoek te worden verricht. Echocardiografie is hierbij van essentieel belang en, met enige beperkingen, ook de hartkatheterisatie.

Gedurende de peri- en postoperatieve periode moet worden gelet op eventueel optredende stoornissen in het prikkelgeleidingssysteem van het hart. Indien dergelijke stoornissen zich voordoen, dient een tijdelijke gangmaker elektrode te worden ingebracht; tevens kan dan een His bundel electrocardiogram worden vervaardigd om de plaats van de geleidingsstoornis te lokaliseren. Indien bij dit onderzoek een verlengd H-V interval wordt gevonden, of indien tijdens het verdere klinische beloop de geleidingsstoornis blijft bestaan of een progressie vertoont, dient een definitief gangmaker systeem te worden geimplanteerd.

Bij patienten met pre-operatieve volumebelasting van de linker ventrikel moet gedacht worden aan pericard vocht als de hart-long ratio gelijk blijft, of toeneemt, blijkens vergelijking van post- en pre-operatieve thorax-foto's.
Indien bij echocardiografisch onderzoek pericardvocht wordt aangetoond en bij tekenen van harttamponade, moet een pericard drainage worden verricht. De duur van de postoperatieve antibiotica behandeling hangt af van de duur van de pre-operatieve behandeling èn van de resultaten van het onderzoek van het peroperatief verwijderde materiaal. Als er aanwijzingen zijn voor infectie, dan dient de postoperatieve antibioticakuur te worden verlengd. Er worden enkele suggesties gedaan om het peroperatief verwijderde materiaal efficiënter te gebruiken.

LIST OF ABBREVIATIONS

a = anterior
Ab = abscess cavity
AC = anterior cusp of pulmonic valve
AB = antibiotic
A(ct) = "active" group
AF = atrial fibrillation
AG = aortic group
A-H = atrial-His interval, as measured on the His bundle electrocardiogram
ALAT = alanine aminotransferase
An = aneurysm
Ao = aorta
AR = aortic regurgitation
AS = aortic stenosis
ASD = atrial septal defect
ASAT = aspartate aminotransferase
AV = aortic valve

Bic = bicuspid aortic valve
Bio = bioprosthesis
Bj-Sh = Björk-Shiley prosthesis

Ch = chordae tendineae
CE = Carpentier-Edwards
CI = cardiac index

D = destruction

ECMV = early closure of mitral valve
e.e. = extra echoes
exc = systolic excursion

fl = fentoliter
FS = fractional shortening

H(ea) = "healed" group
Hb = hemoglobin
HF = heart failure
HLR = heart-lung ratio
Ht = hematocrit
H-V = His-ventricular interval, as measured on the His bundle electrocardiogram

IE = infective endocarditis
IPS = infundibular pulmonic stenosis
IVS = interventricular septum

LA = left atrium
LCC = left coronary cusp
LD = lactate dehydrogenase
LHF = left heart failure
LV = left ventricle
LVEDD = left ventricular end-diastolic dimension
LVESD = left ventricular end-systolic dimension
LVET = left ventricular ejection time
LVOT = left ventricular outflow tract

M = month
MG = mitral group
Mix = mixed group
ML = mitral leaflet
MR = mitral regurgitation
MS = mitral stenosis
MV = mitral valve
Myx = myxoma

N,n,No.,Nr. = number
Nec.ann. = necrotic annulus
NCC = non-coronary cusp
NV = native valve

P = perforation

p = posterior
PC = posterior cusp of pulmonic valve
PM = pacemaker
PuV = pulmonic valve
PV = prosthetic valve
PVV = pulmonary venous vascularity

RA = right atrium
RC = right cusp of pulmonic valve
RCC = right coronary cusp
RCh = ruptured chordae tendineae
RET = relative ejection time
Ret = reticulocyte
RV = right ventricle
RVOT = right ventricular outflow tract

s = septal leaflet of tricuspid valve
SCh = swollen chordae tendineae
SE = subaortic membrane
SR = sinus rhythm

th = thickness
TR = tricuspid regurgitation
TV = tricuspid valve

Vcf = velocity of circumferential fiber shortening
V(eg) = vegetation
VSD = ventricular septal defect

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CURRICULUM VITAE

De schrijver van dit proefschrift werd op 9 september 1941 te Emmen geboren. Hij behaalde in 1960 het eindexamen HBS-B aan het Thorbecke Lyceum te Utrecht. Daarna studeerde hij geneeskunde aan de Rijksuniversiteit te Utrecht, waar in 1966 het doctoraalexamen en in 1969 het artsexamen werd behaald. Vervolgens was hij als dienstplichtig arts gedurende 1 jaar werkzaam op de afdeling interne geneeskunde van het militair hospitaal "Dr. A. Mathijsen", Utrecht (opleider: Dr. C.J. van Belle), waarna hij een jaar als assistent interne geneeskunde was verbonden aan het St. Antonius Ziekenhuis, Utrecht (opleider: Dr. J.G. Verhoeven). Van 1 oktober 1971 tot 1 oktober 1974 volgde hij de opleiding tot cardioloog in het Onze Lieve Vrouwe Gasthuis te Amsterdam (opleider: Dr. A.P.M. Verheugt). Sinds april 1975 is hij verbonden aan de afdeling cardiologie (hoofd: Prof.Dr. J.Th.Ch. Vonk) van het St. Radboud Universiteitsziekenhuis te Nijmegen.

INFECTIVE ENDOCARDITIS AND CARDIAC SURGERY

PROMOTORES: Prof. dr. J.Th.Ch. Vonk
Prof. dr. L.K. Lacquet

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door steun van de Nederlandse Hartstichting.

Gaarne wil ik allen die aan de totstandkoming van dit proefschrift hebben bijgedragen, hartelijk danken.

De tekeningen (met uitzondering van de figuren 3, 4, 5, 6, 7, 18) zijn gemaakt door Marlu Ackermans-de Leeuw en Ed. Noyons, afdeling medische tekenkamer, sektie morfologie. De statistische bewerking van het onderzoek werd verricht door Wil Buys, isotopenafdeling.

STELLINGEN

I

Het beleid bij een patient met endocarditis dient te worden bepaald door de internist en/of de cardioloog, waarbij een nauwe samenwerking met de bacterioloog en, bij cardiale complicaties, de cardiochirurg, van essentieel belang is.

II

De diagnose "infectieuze endocarditis" bij een patient met negatieve bloedkweken, kan pas met zekerheid worden gesteld na bacteriologisch/ microscopisch onderzoek van cardiaal materiaal.

III

De aanwezigheid van klepvegetaties bij echocardiografisch onderzoek vormt op zich geen indicatie voor hartoperatie.

IV

Hoewel een mycotisch aneurysma slechts bij hoge uitzondering door schimmels wordt veroorzaakt, is er de afgelopen 100 jaar niemand in geslaagd om een betere term te bedenken voor een aneurysma, veroorzaakt door een infectieus proces.

V

Ter evaluatie van de effectiviteit van antibioticatherapie voor endocarditis zijn serum bactericidietesten noodzakelijk.

VI

Bij ongecompliceerde, penicilline-gevoelige, streptococcus viridans endocarditis kan worden volstaan met een 2 weken durende penicilline-streptomycinekuur.

VII

Het bij hartoperatie verwijderde materiaal van een patient met (doorgemaakte) endocarditis moet met grote zorg en aandacht worden omringd en gedistribueerd.

VIII

De ambachtelijke kant van de cardiologie, de fysische diagnostiek, behoort samen met de anamnese de basis te blijven waarop het verder geneeskundig handelen rust.

IX

Aan een geperforeerde pacemakerelectrodedraad behoort niet te worden getornd.

X

Electrofysiologisch onderzoek van het hart door middel van geprogrammeerde ventrikelstimulatie verschaft de mogelijkheid om patienten te identificeren met een verhoogde kans op plotselinge hartdood na een doorgemaakt myocardinfarkt.

XI

Glomustumoren van het middenoor manifesteren zich eerder door een synchroon aan de hartslag verlopend kloppend geluid, dan door slechthorendheid.

XII

De achillespeesruptuur kan zonder meer worden gediagnostiseerd met de handgreep van Thompson en dient operatief te worden behandeld.

XIII

Men kan beter arm en warm zijn dan rijk en harteloos.

Strekking van Bomans' sprookje "Het gestolen hart", waarvan een kort citaat.
De jongen keek om zich heen en zag tegen de muren wel honderd glazen kastjes hangen. En in elk daarvan hing een hart, dat klopte.
"Een liefhebberij", zei de duivel achteloos, "ga zitten en vertel me eens: wat kan ik voor je doen?"

Nijmegen, 4 november 1982 K. van Leeuwen